ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE SINGLE-TABLET REGIMEN (EVG/COBI/FTC/TDF, QUAD STR) FOR TREATMENT OF HIV-1 INFECTION IN ADULTS

Antiviral Drugs Advisory Committee Meeting Briefing Document

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

3TC	lamivudine (Epivir®)
ABC	abacavir (Ziagen®)
ABC/3TC	abacavir/lamivudine (Epzicom®)
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANOVA	analysis of variance
APD	action potential duration
AST	aspartate aminotransferase
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated (Atripla®)
ATV	atazanavir (Reyataz®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BCRP	breast cancer resistance protein
BL	baseline
BMD	bone mineral density
BUN	blood urea nitrogen
BSA	body surface area
CD4	cluster of differentiation 4
CG	Cockcroft-Gault
CI	confidence interval
CL_{cr}	creatinine clearance
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
/co	boosted with cobicistat
COBI	cobicistat
Cr	creatinine
CYP	cytochrome P450 enzyme(s)
cysGFR	cystatin C-derived glomerular filtration rate
DAVG	difference between time-weighted average postbaseline and baseline
$DAVG_{xx}$	time-weighted average change from baseline at Week xx
DEXA	dual-energy x-ray absorptiometry
DHHS	(United States) Department of Health and Human Services
DNA	deoxyribonucleic acid
DRV	darunavir (Prezista®)
DRV/co	cobicistat-boosted darunavir

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

DRV/r	ritonavir-boosted darunavir
EACS	European AIDS Clinical Society
EAD	early after-depolarization
ECG	electrocardiogram
ECHO	echocardiogram
EC_{xx}	concentration of a compound inhibiting virus replication by xx%
EE	ethinyl estradiol
EFV	efavirenz (Sustiva®)
EFV/FTC/TDF	efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated (Atripla®)
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation
ESDD	early study drug discontinuation
EU	European Union
EVG	elvitegravir
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated (QUAD)
EVG/r	ritonavir-boosted elvitegravir
FDA	(United States) Food and Drug Administration
FTC	emtricitabine (Emtriva®)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate, coformulated (Complera®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GI	gastrointestinal
Gilead	Gilead Sciences, Inc.
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
HMG CoA	3-hydroxy-3-methyl-glutaryl-CoA
IAS	International Antiviral Society
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IC_{xx}	concentration that results in xx% inhibition
IDMC	independent data monitoring committee
Ig	immunoglobulin (IgG, IgM)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IN	integrase
IND	Investigational New Drug (Application)
INR	international normalized ratio
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
IQR	interquartile range
ISS	integrated summary of safety
ITT	intent-to-treat
LDL	low-density lipoprotein
LPV/r	lopinavir/ritonavir, coformulated (Kaletra®)
LSM	least-squares mean
LV	left ventricular
M1	metabolite of elvitegravir, produced by cytochrome P450-mediated oxidation
M4	metabolite of elvitegravir, produced by glucuronic acid conjugation
MAPD	monophasic action potential duration
MATE	multidrug and toxin extrusion protein
MDZ	midazolam (Versed®)
M=E	missing = excluded
MedDRA	Medical Dictionary for Regulatory Activities
M=F	missing = failure
MH	Mantel-Haenszel
mRNA	messenger ribonucleic acid
N or n	number of subjects in a population (N) or subset (n)
NDA	New Drug Application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PD	pharmacodynamic(s)
PDE5	phosphodiesterase-5
Pgp	P-glycoprotein
PI	protease inhibitor
RTV-boosted PI	ritonavir-boosted protease inhibitor
PK	pharmacokinetic(s)

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PR/RT	protease/reverse transcriptase
PT	preferred term
PXR	pregnane X receptor
Q1, Q3	first quartile, third quartile
QD	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QUAD	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated
/r	boosted with ritonavir
RAL	raltegravir (Isentress®)
RNA	ribonucleic acid
RPV	rilpivirine (Edurant™)
RT	reverse transcriptase
RTV	ritonavir (Norvir®)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TLOVR	time to loss of virologic response
TSH	thyroid stimulating hormone
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of the normal range
US/USA	United States/United States of America
VF	virologic failure
ZDV	zidovudine (Retrovir®)
ZDV/3TC	zidovudine/lamivudine (Combivir®)

PHARMACOKINETIC ABBREVIATIONS

AUC	area under the plasma concentration-time curve
AUC_{0-last}	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda z)$
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval
AUC_{x-xx}	partial area under the plasma concentration versus time curve from time "x" to time "xx"
C_{max}	maximum observed plasma concentration of drug
C_{min}	minimum observed plasma concentration of drug
C_{trough}	observed drug concentration at the end of the dosing interval
E_{max}	maximum (pharmacodynamic) effect

1. INTRODUCTION

On 27 October 2011, Gilead Sciences, Inc. (Gilead) submitted a New Drug Application (NDA) to the United States (US) Food and Drug Administration (FDA) for a single-tablet regimen (STR) containing a fixed-dose combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF). The proposed indication for the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet (referred to as QUAD throughout this document) is for use once daily as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment naive or who have no known substitutions associated with resistance to the individual components.

Two components of the QUAD STR, EVG and COBI, are new chemical entities that were coformulated with the "preferred" standard-of-care (as per the US Department of Health and Human Services [DHHS] Guidelines for Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents) dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone FTC/TDF (Truvada® [TVD], a fixed-dose combination of FTC and TDF), which is also recommended for use once daily. The EVG tablet is being developed for use with a ritonavir (RTV)-boosted protease inhibitor (PI) and other antiretroviral agents in treatment-experienced adults with HIV-1 infection. In addition, a development program is ongoing to evaluate an individual presentation of the COBI tablet as a pharmacoenhancer of the HIV-1 PIs atazanavir (ATV; Reyataz®) and darunavir (DRV; Prezista®). Separate NDAs for these single-agents will be submitted to the FDA in the second quarter of 2012. The development programs and timing of submissions of the NDAs for QUAD, COBI, and EVG were the subject of extensive discussions and agreement with the Division of Antiviral Drug Products at FDA. The QUAD STR was developed as a complete, once-daily, HIV-1 treatment regimen and is not recommended for use in combination with other antiretroviral agents. Safety data from clinical studies of single-agent EVG or COBI with antiretroviral-treatment regimens that differ from those of the QUAD STR are briefly discussed in this document. Safety data from the ongoing studies with EVG or COBI individual agents were submitted in the safety update to the QUAD NDA on 03 February 2012.

EVG is a new chemical entity that belongs to the new class of HIV-1 integrase strand-transfer inhibitors (INSTIs) and is metabolized via cytochrome P450 (CYP) enzymes of the CYP3A family. Coadministration of EVG with a potent CYP3A inhibitor (booster) enables its once-daily administration. COBI, a mechanism-based inhibitor of CYP3A, was developed as a pharmacoenhancer of EVG in the QUAD STR. COBI is an analog of the HIV PI ritonavir that was specifically designed to be devoid of anti-HIV-1 activity, thereby enabling use of once-daily EVG without RTV in the treatment-naive population. Low-dose RTV has the potential to select for PI-resistant virus when used as a pharmacoenhancer of EVG in the absence of a fully-active PI.

The efficacy and safety of the current-marketed products, Viread® (TDF), Emtriva® (FTC), and Truvada, in combination with other antiretroviral agents for the treatment of HIV-1

infection were established at the time of the initial approvals of these agents in 2001, 2003, and 2004, respectively. Collectively, Viread, Emtriva, and Truvada (ie, FTC and TDF, either as single agents or in combination products) provide ~5 million patient-years of TDF exposure and ~3 million patient-years of FTC exposure in the commercial and clinical study settings, and ~9 million patient-years of TDF exposure and ~4 million patient-years of FTC exposure when exposure from the Gilead Access Program is included. The long-term safety profile of these products has been well characterized (refer to the Truvada prescribing information in Appendix 1).

The development goal for the QUAD STR was to demonstrate the efficacy and safety of this unique STR and thereby provide HIV-1 infected adult patients with the option of taking a once-daily INSTI-based STR. An extensive clinical development program demonstrated robust efficacy and safety of the QUAD STR in treatment-naive adults with HIV-1 infection and satisfies regulatory requirements for registration with 2 adequate and well-controlled pivotal studies. An overview of clinical data from this development program is presented in this document, including data from one Phase 2 and two Phase 3 studies conducted with the QUAD STR.

This document provides background information on the QUAD STR for the FDA advisory committee meeting on 11 May 2012. A summary of the data supporting the QUAD NDA is presented in the executive overview. Details on the development of the QUAD STR, the clinical program, and the benefit/risk profile are presented in subsequent sections.

2. EXECUTIVE OVERVIEW

2.1. The Rationale for Development of the QUAD STR

2.1.1. Treatment Landscape for HIV-1 Infection in Adults in the US

HIV-1 infection is a serious and life-threatening disease that is of major public health interest in the US. There are approximately 1.1 million people in the US living with HIV-1 (34 million people worldwide) {15971}, {19661}. If left untreated or suboptimally treated, the infection is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, and ultimately results in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {2537}, {5125}, {8284}.

The primary goals of antiretroviral therapy for HIV-1 infection are to reduce HIV-associated morbidity, prolong duration and quality of life, restore and preserve immunologic function, maximally and durably suppress plasma HIV-1 viral load, and prevent HIV transmission. The US DHHS guidelines for Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents suggest that preferred initial therapy for antiretroviral treatment-naive HIV-1 infected patients consists of 2 NRTIs/NtRTIs and either the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV; Sustiva®), 1 of 2 boosted PIs—darunavir (DRV; Prezista®) or atazanavir—or the INSTI raltegravir (RAL; Isentress®). The US DHHS guidelines list FTC (Emtriva) and TDF (Viread) as the preferred dual NRTI/NtRTI backbone in an antiretroviral regimen for initial therapy {20239}.TDF and FTC, the NRTI components of the QUAD STR, were developed by Gilead and have been approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in the US, the European Union (EU), and other markets worldwide. TDF and FTC are also coformulated as Truvada and both drugs are also part of the STRs Atripla® (ATR; EFV/FTC/TDF) and Complera® (FTC/rilpivirine [RPV; Edurant®]/TDF) for the treatment of HIV-1 infection.

Although HAART has dramatically improved the prognosis of patients infected with HIV-1, eradication of the virus is not possible with currently available therapies. Long-term viral suppression and prevention of drug resistance are goals of successful therapy. Adherence is known to be paramount in maintaining viral suppression, as missing a small number of doses can result in virologic rebound and development of resistance. In regimens of comparable efficacy, the total pill burden, dosing frequency, and concerns about safety and side effects are generally the most significant obstacles to achieving high rates of adherence {4266}, {4256}.

NNRTIs are widely used in the treatment of HIV-1 infection; however, they are associated with safety and tolerability concerns such as hepatotoxicity, central nervous system (CNS) symptoms, rash, and/or the risk of teratogenicity {20239}.

Advantages of RTV-boosted PI-based regimens include excellent virologic potency and a high barrier for development of drug resistance (ie, requires multiple mutations). However, RTV-boosted PIs may be associated with metabolic complications such as dyslipidemia, lipodystrophy, and insulin resistance and have the potential for multiple drug interactions due to metabolism via hepatic enzymes {19048}, {15873}, {14110}. The use of RTV-boosted PIs is hampered by the additional pill burden, tolerability issues, and potential for off-target activity (ie, effects on enzymes other than CYP3A) with RTV.

RAL is the only INSTI approved for use in adults. It requires twice-daily dosing, a regimen recently confirmed by the early termination of a study (QDMRK study) comparing once-daily with twice-daily RAL use that showed a lower response rate, higher virologic failure (VF), and higher resistance in subjects with viral loads > 100,000 copies/mL when administered once daily {19639}. RAL has fewer drug-related adverse events (AEs) and lipid changes than EFV, does not require boosting, and has fewer drug-drug interactions than other NNRTI- and boosted PI-based regimens {18376}.

High rates of efficacy have been demonstrated with standard-of-care regimens. Historical results from Phase 3 studies of EFV-plus-NRTI-containing regimens in treatment-naive subjects demonstrated virologic responses (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) of approximately 80% at Week 48 {17522}, {17599}. Results from a Phase 3 study of RTV-boosted ATV (ATV/r)-plus-NRTI-containing regimens in treatment-naive subjects demonstrated virologic responses (HIV-1 RNA < 50 copies/mL) of 78% at Week 48 {14695}. Results from a Phase 3 study of RAL in treatment-naive subjects demonstrated virologic responses (HIV-1 RNA < 50 copies/mL) of 86% at Week 48 {14246}.

The treatment landscape for HIV-1 infection in adults in the US is discussed in detail in Section 3.1.1.

2.1.2. STRs in the Treatment of HIV-1 Infection

Benefits of STRs

Studies have shown that a once-daily STR (Atripla) significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {13840}, {15302}, {15951}, {15415}. In a study in which subjects taking an initial regimen with multiple pills switched to a simplified single-tablet once-daily regimen, patients had significant improvement in preference of current regimen to their prior regimen (85% at Week 48 compared with 64% at Week 4). In this study, 89% of subjects had ≥ 95% adherence and the vast majority of subjects described their regimen as “very easy to take”: 97% at Week 48 on the STR compared with 81% on their original regimen ($p < 0.0001$) {13840}. In another study, adherence significantly improved from 93.8% to 96.1% ($p < 0.01$) and overall quality of life improved from 68.8% to 72.7% ($p = 0.042$) when subjects’ regimens were substituted with an STR. In this study, the subjects with the lowest percentiles of quality of life also had worse adherence compared with the subjects in the highest percentiles in every way measured: doses in the last month (92.9% vs 98.5%), doses in the last month taken at the correct time (82.6% vs 97.3%), doses taken in the last week

(94.8% vs 98.6%), and doses in the last week taken at the correct time (85.2% vs 97.7%) {15951}. In a study in the hardest-to-treat subjects in a homeless population in San Francisco, treatment with an STR resulted in significantly improved adherence (13% difference favoring STR, p = 0.001) and improved virologic suppression (23% difference favoring STR, p = 0.02) {15415}, {16661}.

In a national data base review of more than 7073 HIV patients with commercial insurance, patients taking an STR were 59% more likely to achieve 95% adherence compared with those taking 3 or more pills per day. In addition, patients who received an STR were 24% less likely to have a hospitalization compared with those who received 3 or more pills per day {20207}. Another study also found that STRs were associated with a 25% reduced risk of hospitalization, a 17% reduction in total healthcare cost including reduced inpatient and outpatient costs, and reduced monthly out-of-pocket pharmacy expenditures {18702}, {18900}.

Limitations of Current STRs

To date, there are 2 STRs (both containing an NNRTI and Truvada) approved for once-daily administration in the treatment of HIV-1 infection: Atripla and Complera.

Atripla contains EFV, which has been associated with CNS symptoms including dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations, which occurred in 53% of subjects compared with 25% in comparator arms in EFV registrational studies. These CNS symptoms led to EFV discontinuation in 2.1% of patients in registrational studies and up to 13% in a retrospective study {18921}, {20251}. EFV has also been associated with new onset skin rashes in 26% of patients compared with 17% in control groups {18921}. The skin rash led to discontinuation of EFV in 1.7% of patients {18921}. In Study ACTG5202, EFV was associated with greater increase in total cholesterol and low-density lipoprotein (LDL) cholesterol compared with ATV/r, regardless of the NRTI backbone (abacavir/lamivudine or FTC/TDF), which has implications for long-term cardiovascular risk {19273}. In addition, EFV is classified as a teratogen (Pregnancy Category D: positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans). The Atripla Prescribing Information states that, “Pregnancy should be avoided in women taking Atripla.” The pregnancy risk occurs in the first trimester and can cause fetal harm before a patient is aware of her pregnancy; therefore Atripla has limited use in women of childbearing potential {18921}.

Complera contains RPV, for which the incidence of both virologic failure and resistance was higher in subjects with high baseline viral load (HIV-1 RNA > 100,000 copies/mL). Complera also must be taken with food, but cannot be taken with proton pump inhibitors {18319}. There are currently no approved STRs that combine either a PI or an INSTI with an NRTI backbone into a once-daily tablet.

The use of NNRTI-based STRs is also limited by the presence of transmitted NNRTI resistance mutations in newly infected patients. Approximately 8% of antiretroviral treatment-naive patients have been shown to harbor NNRTI resistance {20246}.

Therefore, there remains a need for alternative STRs with potent and sustained efficacy with a favorable tolerability and safety profile across the different subgroups (eg, age, sex, race, baseline HIV-1 RNA level, and baseline cluster of differentiation 4 [CD4] cell count) of the HIV-1 infected patient population.

2.1.3. The QUAD STR

Gilead has developed an STR that contains a fixed-dose combination of EVG, COBI, FTC, and TDF: the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet (referred to as QUAD throughout this document).

- EVG is a new chemical entity that belongs to the class of HIV-1 INSTIs that prevent integration of HIV-1 genetic material into the host-cell genome and displays potent in vitro anti-HIV activity. It is the second-in-class INSTI (after RAL). Initial clinical studies in healthy volunteers (Study GS-US-183-0102) and HIV-1 infected patients (Study GS-US-183-0101) showed that coadministation of EVG with a potent CYP3A inhibitor/pharmacoenhancer (“booster”) substantially increases its systemic exposures, including maintenance of high trough concentrations (which is best associated with antiviral activity), allowing once-daily administration.

- COBI is a potent and selective mechanism-based inhibitor of CYP3A enzymes and a pharmacoenhancer of EVG, which is a CYP3A substrate. COBI is also a novel structural analog of RTV that was specifically designed to be devoid of anti-HIV-1 activity, thereby enabling administration of COBI as a pharmacoenhancer of EVG in the treatment-naive population. COBI is also more amenable than RTV for coformulation with other agents and is a more selective inhibitor of CYP3A with fewer off-target effects (inhibition or induction) on other CYP or Phase 2 metabolizing enzymes.

- FTC (Emtriva) is an NRTI that is marketed as a once-daily capsule (200 mg) and as an oral solution (10 mg/mL). FTC is a synthetic analog of the naturally occurring pyrimidine nucleoside, 2′-deoxycytidine, that is structurally similar to lamivudine. Intracellularly, FTC is phosphorylated by cellular enzymes to form the active metabolite, emtricitabine triphosphate. The registration of FTC for the treatment of HIV-1 infection in adult and pediatric patients was supported by an extensive program of clinical studies in healthy subjects and HIV-infected subjects, which provided detailed assessments of its pharmacokinetics, pharmacodynamics, potential drug-drug interactions, and clinical efficacy and safety.

- TDF (Viread), the oral prodrug of tenofovir (TFV), is an NtRTI that is marketed as a once-daily, film-coated, 300-mg tablet. After absorption, TDF is rapidly converted to TFV, which is metabolized intracellularly to the active metabolite, tenofovir diphosphate. The registration of TDF for the treatment of HIV-1 infection was supported by an

extensive program of clinical studies in healthy subjects and HIV-infected subjects, which provided detailed assessments of its pharmacokinetics, pharmacodynamics, potential drug-drug interactions, and clinical efficacy and safety. Postmarketing reports indicate that bone abnormalities (infrequently contributing to fractures) and renal adverse reactions may be associated with TDF use.

The QUAD tablet is the first STR that combines an HIV integrase strand-transfer inhibitor with the US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada) {20239}. The QUAD STR has demonstrated potent and durable antiretroviral activity (Section 7), a favorable safety and tolerability profile (Section 8), and has the additional benefit of being a complete, once-daily antiretroviral regimen. The safety of TDF and FTC has been well characterized with ~9 and ~4 million patient-years, respectively. The frequency of resistance development in subjects taking the QUAD STR was low (Section 7.2). The QUAD STR is a valuable addition to the current armamentarium of approved antiretrovirals (including the STRs Atripla and Complera, and PI- and RAL-based regimens) for the following reasons:

NNRTI-based regimens:

- Unlike Atripla (Pregnancy Category D), the QUAD STR is proposed as Pregnancy Category B because none of the components have shown direct or indirect harmful effects with respect to pregnancy and embryonal/fetal development in animal studies.

- Unlike Complera, the QUAD STR displayed potent and durable antiviral suppression regardless of baseline viral load.

- In clinical studies, a significantly lower percentage of subjects receiving QUAD compared with subjects receiving Atripla reported any neurological/psychiatric AE (based on a prespecified analysis).

- In clinical studies, significantly lower mean increases from baseline in fasting total cholesterol and LDL were observed in subjects receiving QUAD compared with subjects receiving Atripla.

RTV-boosted PI-based regimens:

- PIs can be associated with metabolic complications such as dyslipidemia, lipodystrophy, and insulin resistance {15873}, {14110}, {19048}. The QUAD STR had lower mean increases from baseline in fasting triglycerides compared with ATV/r+TVD.

- The QUAD STR had lower bilirubin-related AEs compared with ATV/r+TVD.

- The QUAD STR provides treatment-naive patients the opportunity to take a highly effective regimen as a once-daily tablet, whereas the use of PIs is hampered by the additional pill burden associated with the need to coadminister low-dose RTV, and the absence of coformulations with NRTI/N(t)RTI backbones.

RAL-based regimens:

- The QUAD STR is an INSTI-based STR with potent activity and efficacy across low and high viral loads as a once-daily regimen. RAL requires twice-daily dosing, as demonstrated in the QDMRK study comparing once-daily with twice-daily RAL use that showed a lower response rate, higher VF, and higher resistance in subjects with viral loads >100,000 copies/mL when administered once daily {19639}.

- RAL is not available within a fixed-dose combination or STR and has additional pill burden.

The QUAD STR is discussed in detail in Section 3.1.3.

2.2. Regulatory History and Proposed Indication Statement

The QUAD STR contains a fixed-dose combination of EVG and COBI, and 2 marketed products, FTC and TDF: the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet.

The efficacy and safety of the marketed products Emtriva, Viread, and Truvada in combination with other antiretroviral agents for the treatment of HIV-1 infection have been established through comprehensive programs of nonclinical and clinical studies with these medicinal products. The safety profile of these products has also been well characterized through extensive postmarketing experience (refer to the Truvada prescribing information in Appendix 1). A notable toxicity of TDF is proximal renal tubulopathy, which may warrant treatment discontinuation in a small number of patients (~1%); this is well understood by HIV health-care providers, readily assessed by simple laboratory tests, and reversible upon drug discontinuation (Section 8.7.1).

Investigational New Drug (IND) Applications for EVG, COBI, and the QUAD STR were originally submitted on 15 April 2005, 06 March 2008, and 28 July 2008, respectively.

The development program for the QUAD STR was granted fast-track designation by the FDA on 01 December 2010. Gilead submitted an NDA for the QUAD STR on 27 October 2011 (NDA 203-100). The principal clinical safety and efficacy data supporting the NDA were derived from one Phase 2 study (GS-US-236-0104) and two Phase 3 studies (GS-US-236-0102 and GS-US-236-0103) conducted with the QUAD STR in antiretroviral treatment-naive, HIV-1 infected adult subjects. The primary endpoint was met in both of the Phase 3 studies, thereby supporting the following proposed indication:

> [TRADENAME] is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment naive or who have no known substitutions associated with resistance to the individual components of [TRADENAME].

Pending regulatory approval, QUAD would be the first INSTI-based STR for the treatment of HIV-1 infection.

The regulatory history of the QUAD STR is discussed in detail in Section 3.2.

2.3. Overview of the Clinical Development Program for the QUAD STR

The goal of the development plan for the QUAD STR was to provide HIV-1 infected adult patients with the option of taking a once-daily INSTI within an STR containing US DHHS-preferred NRTI/NtRTIs.

EVG is a low molecular weight, HIV-1 INSTI that prevents integration of the HIV-1 genetic material into the host-cell genome. The pharmacokinetic/pharmacodynamic (PK/PD) relationships of EVG antiviral activity/efficacy leading to Phase 3 dose selection were investigated in a proof-of-concept, short-term (10 days) monotherapy study and as a part of an antiretroviral regimen in treatment-experienced HIV-1 infected subjects in a Phase 2 study (GS-US-183-0105). As monotherapy, EVG exhibited PK and PD that supported once-daily dosing in the boosted state (100 mg of the PI RTV) with high trough concentrations, which were best associated with antiviral activity. Based on these PK/PD results, the decision was made to develop EVG as a "boosted drug" and identify a once-daily dose that would be associated with a robust antiviral response, amenable to coformulation, would provide PK compatibility with partner NRTIs, and would be less impacted by late or missed dosing. Additional studies were performed using RTV to "boost" EVG.

RTV, an HIV-1 PI, is an efficient mechanism-based inhibitor of CYP3A that significantly boosts CYP3A substrates, including EVG. Liabilities of low-dose RTV include the following: gastrointestinal (GI) AEs that are problematic for some patients even at lower boosting doses; the potential for metabolic complications, including elevations in serum cholesterol and triglycerides; and insulin resistance in some patients {11025}. In addition, low-dose RTV has the potential to select for PI-resistant virus when used as a pharmacoenhancer of EVG in the absence of a fully-active PI.

Because of the limitations of RTV, Gilead developed a new chemical entity, COBI, to boost EVG as part of the QUAD STR. COBI is also a mechanism-based CYP3A inhibitor but without anti-HIV activity, which therefore enables use of EVG in treatment-naive patients without a fully-active PI. In a first-in-human clinical study (GS-US-216-0101), COBI was well tolerated at doses up to 200 mg once daily, with favorable PK and PD as shown by its ability to reduce the first-pass metabolism and clearance of the probe CYP3A substrate midazolam (MDZ; Versed®) to levels similar to that achieved by RTV 100 mg in healthy subjects.

Gilead conducted Phase 1 and 2 studies to support the use of COBI as a "booster" for EVG, and to characterize the PK and safety of all the components following administration of the QUAD STR. An extensive clinical development program, including one Phase 2 study (GS-US-236-0104) and 2 adequate and well-controlled Phase 3 studies (GS-US-236-0102 and GS-US-236-0103), was conducted with the QUAD STR. In addition, an ongoing Phase 3 study is being conducted to evaluate COBI-containing regimens, including the QUAD STR, in HIV-1 infected subjects with mild-to-moderate renal impairment (GS-US-236-0118). Overall, 749 HIV-1 infected subjects were exposed to the QUAD STR in the randomized phases of the Phase 2 and 3 studies.

Gilead is also developing the EVG tablet for use with an RTV-boosted PI and other antiretroviral agents in treatment-experienced adults with HIV-1 infection, and the COBI tablet as a pharmacoenhancer of the HIV-1 PIs ATV and DRV. The development of COBI and EVG is supported by Phase 2 and Phase 3 studies (EVG: Phase 2 Study GS-US-183-0105 and Phase 3 Study GS-US-183-0145 [Section 8.18.1.1], COBI: Phase 2 Study GS-US-216-0105 and Phase 3 Study GS-US-216-0114 [Sections 2.7.6, 8.7, and 8.18.2]).

To date, across the QUAD STR, COBI tablet, and EVG tablet development programs, a total of approximately 1800 and 2600 adult subjects were exposed to COBI and EVG, respectively, either as single agent or as part of the QUAD STR. A total of 898 subjects received the QUAD STR (126 subjects in Phase 1 studies and 772 subjects in Phase 2 or 3 studies), 958 subjects received COBI tablets (564 subjects in Phase 1 studies and 394 subjects in Phase 2 or 3 studies), and 1693 subjects received EVG tablets (1064 subjects in Phase 1 studies and 629 subjects in Phase 2 or 3 studies) (Table 3).

The clinical development program for the QUAD STR is discussed in detail in Section 3.3.

2.4. Summary of the Nonclinical Program

Comprehensive programs of nonclinical studies with EVG, COBI, FTC, TDF, and TFV have been conducted, including primary and secondary PD, safety pharmacology, PK, and toxicology studies. A number of key studies were conducted using the combination of EVG and COBI, FTC and TDF, and EVG/COBI/FTC/TDF. The overall program, including the data from the combination and individual agent studies, is complete as per International Conference on Harmonization/FDA Guidance (ICH M3[R2] January 2010) and supports the favorable benefit/risk profile of the QUAD STR.

Nonclinical data for FTC and TDF are presented in their respective US prescribing information (Emtriva {12644}, Viread {16282}, and Truvada: Appendix 1) and will not be discussed in detail in this document.

The nonclinical development program for the QUAD STR is discussed in detail in Section 4.

2.4.1. In Vitro Antiviral Activity

The HIV-1 INSTI EVG has potent antiretroviral activity against wild-type laboratory and clinical isolates of HIV-1, against HIV-1 B or non-B subtypes, and against HIV-1 with drug resistance mutations of the NNRTI, NRTI, and PI classes. The HIV-1 NRTIs FTC and TFV have potent antiretroviral activity against wild-type laboratory and clinical isolates of HIV-1, against HIV-1 B or non-B subtypes, and against HIV-1 with drug resistance mutations of the NNRTI and PI classes, and to some isolates with NRTI resistance mutations. TDF and FTC also have anti-hepatitis B virus (HBV) activity. In addition, the combination of EVG, FTC, and TFV in 3-drug combination experiments showed synergistic anti-HIV-1 activity. Synergistic anti-HIV-1 activity was maintained in vitro for EVG/FTC/TFV when tested with COBI, showing no unexpected intracellular antagonism.

EVG has no in vitro antiviral activity against HBV or hepatitis C virus (HCV). COBI has no in vitro antiviral activity against HIV-1, HBV, or HCV, and does not antagonize the in vitro antiviral effects of EVG, FTC, or TFV (Section 4.1.1).

2.4.2. Resistance

HIV-1 isolates with reduced susceptibility to EVG have been selected in cell culture. Reduced susceptibility to EVG was most commonly associated with the primary integrase substitutions T66I, E92Q, and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K. EVG showed cross-resistance in vitro to the RAL-selected substitutions T66A/K, Q148H/K, and N155H.

No in vitro resistance can be demonstrated with COBI due to its lack of antiretroviral activity (Section 4.1.1).

2.4.3. Pharmacokinetics

EVG is primarily eliminated by oxidative metabolism by CYP3A (the major route) and by glucuronidation (minor route) by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and 1A3. COBI is a potent, mechanism-based inhibitor of human CYP3A enzymes. When combined, COBI causes the intended reduction in EVG clearance through inhibition of CYP3A-mediated metabolism. EVG is a weak inducer of CYP3A in vitro, but effects on this enzyme in vivo are masked by the inhibitory effect of COBI. TFV and FTC, the NRTI components of QUAD, are not metabolized by CYP3A and are eliminated renally, primarily as unchanged drug via filtration and also renal transport pathways that are not inhibited by COBI. Therefore, coadministration with COBI and EVG does not affect their elimination.

The potency and mechanism of CYP3A inhibition by COBI is similar to RTV. Relative to RTV, COBI shows higher specificity for inhibition of CYP3A with weak inhibition of CYP2D6 and no inhibition of other CYP enzymes or UGT1A1. COBI has a comparable transporter inhibition profile to that of RTV. Compared with RTV, COBI is a markedly weaker inducer of drug metabolizing enzymes, with a low potential for induction-driven drug interactions.

Similar to RTV, COBI is a transient inhibitor of intestinal efflux transporters and may cause modest increases in the intestinal absorption of concomitant medications that are substrates for intestinal P-glycoprotein (Pgp) or the breast cancer resistance protein (BCRP) such as TDF. COBI and RTV have been found to reversibly inhibit the organic cation transport (OCT) pathway (multidrug and toxin extrusion protein [MATE] 1) responsible for creatinine secretion in the kidney. COBI and RTV do not inhibit the active tubular secretion of organic anions, including TFV, at clinically relevant exposures (Section 4.2).

2.4.4. Nonclinical Safety

Comprehensive nonclinical toxicology programs with EVG, COBI, FTC, and TDF have been completed. These studies have characterized the acute toxicity, subchronic/chronic toxicity,

mutagenicity, carcinogenicity, and reproductive toxicity of each of the individual agents, and the toxicity of EVG/COBI and FTC/TDF combinations.

EVG, FTC, and TDF do not have significant undesirable pharmacologic activity as determined by a variety of in vitro and in vivo safety pharmacology studies. Patch clamp studies indicate that COBI inhibits the hERG potassium current (concentration that results in 50% inhibition [IC_{50}] 1.8 µM) and the L-type calcium channel (IC_{50} 6 µM). Results from a Purkinje fiber assay, 2 Langendorff studies with isolated rabbit hearts, a cardiovascular study in dogs, and electrocardiogram (ECG) evaluations in repeat-dose toxicity studies in dogs show that COBI has a low potential for QT prolongation, but may have a tendency to slightly prolong the PR interval. These effects, including the shortening of the action potential duration (APD) in rabbit Purkinje fibers, the negative inotropic effects in isolated rabbit hearts, and the mild delay in the PR interval in dogs, may be a consequence of COBI interaction with cardiac calcium channels. In clinical studies, including a thorough QT study with COBI doses/exposures (AUC_{tau}) ~2- or 4-fold above therapeutic dose/exposures, no clinically significant changes in ECGs or left ventricular (LV) function (assessed by echocardiogram [ECHO]) have been observed with COBI administered as an individual agent, or within the QUAD STR (Section 8.15).

The toxicity profiles of the 4 agents differ substantially, with no clinically significant overlapping toxicity. Nonclinical studies with EVG have not identified any specific target organ toxicities or cause for concern. Target organs identified for COBI were liver (mouse, rat, and dog) and thyroid (rat). (Note: In contrast to its specific CYP3A inhibitory effect in humans, COBI is a reversible CYP3A inhibitor in rodents, dogs, and monkeys. Further, in rodents, COBI is an inducer via activation of the rodent pregnane X receptor [PXR] with consequent marked induction of CYP3A and other PXR-related proteins.) Liver effects were qualitatively similar across species, and considered adaptive, nonadverse changes {17078}, {18407}. Similarly, thyroid changes were rat specific (secondary to PXR activation, hepatic microsomal enzyme induction, and thyroid hormone imbalance), and predispose rats, but not humans, to thyroid neoplasms; it is unlikely that COBI presents a risk to the human thyroid {11926}, {11927}, {11933}. No clinically-relevant effects on thyroid hormones have been observed in clinical studies with the QUAD STR (Section 8.13). Other potential toxicities (clinical pathology changes; lower immunoglobulin G [IgG] antibody titers that were noted in 1 study in female rats only) were not identified in clinical studies with the QUAD STR (Section 8.14). For FTC, the only toxicity observed in chronic animal studies was mild, reversible anemia at large multiples of clinical exposure; therefore, these hematological findings are not considered relevant to clinical use. FTC has an established clinical safety profile with no significant toxicities observed. The principal target organs of toxicity in rats, dogs, and non-human primates following oral administration of TDF were the kidney (karyomegaly, tubular degeneration) and bone (decreased bone mineral density), with GI tract changes noted only in rodents. The renal and bone findings correlate with the known clinical toxicities for TDF. Combination toxicity studies with EVG and COBI, and FTC and TDF did not reveal any new or additive toxicities.

In long-term carcinogenicity studies of EVG, there were no drug-related increases in tumor incidence in mice or in rats. In long-term carcinogenicity studies of COBI in mice, no

drug-related increases in tumor incidence were observed. In rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was noted. The follicular cell findings are considered to be rat specific, secondary to species-specific activation of PXR, hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans {11927}, {11933}. Pharmaceuticals that induce liver microsomal enzymes and disrupt thyroid function in rats include several approved products for the treatment of HIV-1 infection (eg, ritonavir, lopinavir, atazanavir, darunavir, fosamprenavir, nelfinavir, nevirapine, and tipranavir), CNS-acting drugs (eg, phenobarbital and benzodiazepines), calcium channel blockers (eg, nicardipine and bepridil), steroids (eg, spironolactone), and retinoids {11931}, {11926}, {11923}, {13467}, {11927}, {11924}. (Note: The COBI carcinogenicity study data became available after the submission of the QUAD NDA and safety update, and have been submitted to the QUAD IND).

EVG, COBI, FTC, and TDF have not shown significant adverse effects in reproductive and developmental toxicity studies, including studies to assess fertility, embryo-fetal development, and pre- and postnatal development.

The nonclinical profile of the individual agents, the lack of notable overlapping toxicity in animals, and clinical data with EVG, COBI, and the QUAD STR support the overall benefit/risk profile of this INSTI-based STR for HIV-1 infection (Section 4.3).

2.5. Clinical Pharmacology

EVG is an HIV INSTI that has been coformulated with COBI, FTC, and TDF as the QUAD STR for the treatment of HIV-1 infected adults. Given its primarily CYP3A-mediated metabolism, early clinical development of EVG evaluated coadministration with RTV 100 mg, which resulted in substantial (20-fold) boosting of EVG exposures and 3-fold longer plasma half-life (9 hours vs 3 hours for boosted vs unboosted), allowing once-daily boosted-EVG administration and maintenance of high EVG trough concentrations, which are best associated with its antiviral activity. COBI 150 mg-boosted EVG exposures are equivalent to those achieved with RTV-boosted EVG (EVG/r), resulting in EVG trough concentrations ~10-fold above the protein binding adjusted 95% effective concentration (EC_{95}). The QUAD STR was administered in Phase 1, 2, and 3 studies with food due to higher EVG oral bioavailability under fed conditions {8819}.

The exposure-response profile for EVG has been well characterized. Based on monotherapy and Phase 2 studies in subjects infected with HIV-1 that evaluated EVG at multiple unboosted and boosted doses over a wide exposure range (~20-fold), boosted-EVG 150 mg equivalent exposures were in the plateau phase of the exposure-response relationship and corresponded to near-maximal efficacy. In the Phase 3 studies, the QUAD STR was associated with high and comparable rates of virologic efficacy (89% and 87% in lowest and highest EVG C_{trough} quartiles, respectively) and no trends in incidence of common AEs were observed over the range of EVG exposures.

The potential for the QUAD STR to undergo clinically relevant drug interactions has been well characterized. The intended PD effect of COBI (ie, CYP3A inhibition) results in higher

exposures of concomitant medications metabolized by this pathway. COBI is a transient inhibitor of intestinal efflux transporters, resulting in modest increases in the intestinal absorption of concomitant medications whose intestinal absorption is limited by Pgp or BCRP. Accordingly, the intestinal efflux of TDF, a Pgp substrate, is reduced by COBI, and results in modestly higher (~26%) TFV plasma exposures (AUC) following administration of QUAD. These higher TFV exposures are comparable with those seen when a TDF-containing regimen is administered with other antiretrovirals that are intestinal Pgp inhibitors such as RPV or RTV, including RTV-boosted PIs (eg, increase in TFV plasma exposure ~24% with RPV, ~37% with ATV/r, ~22% with DRV/r, and ~32% with lopinavir [LPV]/r) {8510}, {11255}. COBI has been shown to increase serum creatinine. Study GS-US-216-0121 evaluated this effect in HIV-1 negative subjects with normal (estimated glomerular filtration rate [eGFR] ≥ 80 mL/min) or mild-to-moderate renal impairment (GFR 50 to 79 mL/min). Following 7 days of dosing with COBI in subjects with normal renal function (eGFR ≥ 80 mL/min), median (Q1, Q3) serum creatinine change from baseline was 0.11 mg/dL (0.03, 0.15) relative to baseline; serum creatinine returned to baseline when study drug was discontinued (0.02 mg/dL [−0.04, 0.06]). Following 7 days of dosing with COBI in subjects with mild/moderate renal impairment (GFR 50 to 79 mL/min), median (Q1, Q3) serum creatinine change from baseline was 0.28 mg/dL (0.11, 0.33) relative to baseline, consistent with the greater relative contribution of secretion to overall creatinine clearance in this population compared with normal renal function; serum creatinine returned to baseline when study drug was discontinued (0.04 mg/dL [0.00, 0.08]). Importantly, COBI did not affect actual GFR (aGFR) assessed via the clearance of a GFR probe substrate iohexol.

Clinical pharmacology is discussed in detail in Section 5.

2.6. Overview of Principal Studies for the QUAD STR

The principal studies for the QUAD STR are Phase 2 Study GS-US-236-0104 and Phase 3 Studies GS-US-236-0102 and GS-US-236-0103. Study populations were antiretroviral treatment-naive, HIV-1 infected subjects with HIV-1 RNA ≥ 5000 copies/mL at screening, with no prior use of any approved or experimental antiretroviral drug. In all 3 studies, randomization was stratified by HIV-1 RNA at screening (≤ 100,000 copies/mL or > 100,000 copies/mL). In these 3 studies, the comparator arm contained the US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada) and a preferred third agent (ie, the NNRTI EFV [given as the Atripla STR] in GS-US-236-0104 and GS-US-236-0102, and ATV/r in GS-US-236-0103). The Phase 2 and 3 clinical development program for the QUAD STR is discussed in detail in Section 6.1.

2.6.1. Phase 2 and 3 Studies GS-US-236-0104, GS-US-236-0102 and GS-US-236-0103

Phase 2 Study GS-US-236-0104 is described in Section 6.1.1.1. Studies GS-US-236-0102 and GS-US-236-0103 are ongoing (double-blind phase) Phase 3, double-dummy, randomized, double-blind, multicenter, multiple-dose, active-controlled studies evaluating the safety and efficacy of the QUAD STR versus the Atripla STR (GS-US-236-0102) and

ATV/r+TVD (GS-US-236-0103) in HIV-1 infected antiretroviral treatment-naive adult subjects. In Study GS-US-236-0102, 707 subjects were enrolled in a total of 102 study sites; 97 in the US and 5 in Puerto Rico. In Study GS-US-236-0103, 715 subjects were enrolled in a total of 146 study sites; 88 in the US and 58 in other countries. In the Phase 3 studies, screening genotype reports were required to show sensitivity to the drugs in the comparator arm (EFV, FTC, and TDF [GS-US-236-0102] or ATV [GS-US-236-0103]).

In Study GS-US-236-0102, a total of 707 subjects were randomized in a 1:1 ratio to either QUAD + ATR placebo or ATR + QUAD placebo. In Study GS-US-236-0103, a total of 715 subjects were randomized in a 1:1 ratio to either QUAD + ATV/r+TVD placebo or ATV/r+TVD + QUAD placebo.

In both studies, the primary efficacy endpoint was the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis (see Appendix 3 for a description of this analysis). The secondary efficacy endpoint was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL based on the FDA-defined time to loss of virologic response [TLOVR] algorithm (see Appendix 3 for a description of this analysis). The 3 studies were well conducted with a loss-to-follow up rate of 2.7% (40/1493 subjects).

The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the QUAD STR compared with the comparator using a conventional 95% confidence interval (CI) approach, with a noninferiority margin of 12%. Both studies are still blinded; however, the 48-week primary endpoints have been analyzed and were included in the QUAD NDA.

2.7. Clinical Study Results

The QUAD STR has demonstrated high rates of virologic success in Phase 3 Studies GS-US-236-0102 and GS-US-236-0103 and Phase 2 Study GS-US-236-0104. The results from the primary efficacy analysis (virologic outcomes using snapshot analysis) for the two Phase 3 studies demonstrated that QUAD once daily was noninferior to Atripla and ATV/r+TVD once daily when administered for 48 weeks to HIV-1 infected antiretroviral treatment-naive adults. Secondary analysis (virologic outcomes using TLOVR analysis) results were consistent with the results of the snapshot analysis. The efficacy results of the QUAD STR were confirmed by multiple sensitivity and subgroup analyses. Taken together, these data highlight the potent and durable efficacy profile of the QUAD STR versus highly active comparators for the treatment of treatment-naive, HIV-1 infected subjects.

Efficacy in Phase 2 Study GS-US-236-0104 is presented in Section 7.1.1. Efficacy in Phase 3 Studies GS-US-236-0102 and GS-US-236-0103 is briefly described below and is discussed in detail in Sections 7.1.2 and 7.1.3, respectively. Comparison of results in subpopulations using pooled data from Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 is discussed below and in Section 7.1.5. Results for the primary efficacy endpoint using pooled data are discussed in Section 7.1.4.

2.7.1. Efficacy in Study GS-US-236-0102

Primary Efficacy Endpoint: Virologic Outcomes at Week 48 using Snapshot Analysis with HIV-1 RNA Cutoff at 50 copies/mL

The results from the primary efficacy analysis demonstrated that QUAD once daily was noninferior to Atripla once daily when administered for 48 weeks to HIV-1 infected, antiretroviral treatment-naive adults (Table 1). Based on the FDA-defined snapshot analysis, 87.6% of subjects (305 of 348) in the QUAD group and 84.1% of subjects (296 of 352) in the Atripla group had virologic success (intent-to-treat [ITT] analysis set). The difference in the percentage of subjects with virologic success was 3.6% (95% CI: −1.6% to 8.8%). Sensitivity analyses to evaluate effects of study drug discontinuations not related to virologic response and late discontinuations also demonstrated that the QUAD STR was noninferior to Atripla. Subgroup analyses (ie, age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count) based on the FDA-defined snapshot analysis revealed high and generally comparable rates of virologic success with those observed for the overall study population (Figure 8).

Secondary Efficacy Endpoint: Virologic Outcomes at Week 48 using TLOVR Analysis with HIV-1 RNA Cutoff at 50 copies/mL

The FDA-defined TLOVR analysis results were consistent with the results of the snapshot analysis, confirming that the QUAD and Atripla STRs had comparable rates of virologic response. Based on the TLOVR analysis, 85.9% of subjects (299 of 348) in the QUAD group and 83.2% of subjects (293 of 352) in the Atripla group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The difference in the percentages of responders at Week 48 was 2.7% (95% CI: –2.6% to 8.1%).

Tertiary Efficacy Endpoint: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using missing = failure (M=F) and missing = excluded (M=E) methods were similar between treatments. In the M=F analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was significantly greater in the QUAD group than the Atripla group from Week 2 through Week 16; response rates between the 2 groups were similar from Week 24 through Week 48. At Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 88.8% (309 of 348) in the QUAD group and 85.5% (301 of 352) in the Atripla group (Figure 6). In the M=E analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 was 95.1% (309 of 325) in the QUAD group and 95.3% (301 of 316) in the Atripla group.

Tertiary Efficacy Endpoint: Change from Baseline in CD4 Cell Count

Mean (standard deviation [SD]) baseline CD4 cell counts were 391 (188.6) cells/µL in the QUAD group and 382 (170.2) cells/µL in the Atripla group. CD4 cell counts increased following administration of study drug, and the mean increases were similar between the

QUAD and Atripla groups, but were numerically higher in the QUAD group at all time points. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 239 (167.2) cells/µL in the QUAD group and 206 (153.4) cells/µL in the Atripla group. The difference in least-squares means (LSMs) from an analysis of variance (ANOVA) model was 33 (95% CI: 8 to 58).

2.7.2. Efficacy in Study GS-US-236-0103

Primary Efficacy Endpoint: Virologic Outcomes at Week 48 using Snapshot Analysis with HIV-1 RNA Cutoff at 50 copies/mL

The results from the primary efficacy analysis demonstrated that QUAD once daily was noninferior to ATV/r+TVD once daily when administered for 48 weeks to HIV-1 infected, antiretroviral treatment-naive adults (Table 1). Based on the FDA-defined snapshot analysis, 89.5% of subjects (316 of 353) in the QUAD group and 86.8% of subjects (308 of 355) in the ATV/r+TVD group had virologic success (ITT analysis set). The difference in the percentage of subjects with virologic success was 3.0% (95% CI: –1.9% to 7.8%). Sensitivity analyses to evaluate effects of study drug discontinuations not related to virologic response and late discontinuations also demonstrated that the QUAD STR was noninferior to ATV/r+TVD. Subgroup analyses (ie, age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count) based on the FDA-defined snapshot analysis revealed high and generally comparable rates of virologic success with those observed for the overall study population (Figure 8).

Secondary Efficacy Endpoint: Virologic Outcomes at Week 48 using TLOVR Analysis with HIV-1 RNA Cutoff at 50 copies/mL

The FDA-defined TLOVR analysis results were consistent with the results of the snapshot analysis, confirming that the QUAD STR and ATV/r+TVD had comparable rates of virologic response. Based on the TLOVR analysis, 86.1% of subjects (304 of 353) in the QUAD group and 84.8% of subjects (301 of 355) in the ATV/r+TVD group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The difference in the percentages of responders at Week 48 was 1.6% (95% CI: –3.6% to 6.8%).

Tertiary Efficacy Endpoint: Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using M=F and M=E methods were similar between treatments. In the M=F analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was significantly greater in the QUAD group than in the ATV/r+TVD group from Week 2 through Week 16; response rates between the 2 groups were similar from Week 24 through Week 48. At Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 91.5% (323 of 353) in the QUAD group and 88.2% (313 of 355) in the ATV/r+TVD group (Figure 7). In the M=E analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 was 96.7% (323 of 334) in the QUAD group and 96.9% (313 of 323) in the ATV/r+TVD group.

Tertiary Efficacy Endpoint: Change from Baseline in CD4 Cell Count

Mean (SD) baseline CD4 cell counts were 364 (180.6) cells/μL in the QUAD group and 375 (158.9) cells/μL in the ATV/r+TVD group. CD4 cell counts increased following administration of study drug, and the mean increases were similar between the QUAD and ATV/r+TVD groups at all time points. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 207 (164.2) cells/μL in the QUAD group and 211 (160.3) cells/μL in the ATV/r+TVD group. The difference in LSMs from an ANOVA model was –6 (95% CI: –31 to 18).

Table 1. GS-US-236-0102 and GS-US-236-0103: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

	GS-US-236-0102		GS-US-236-0103	
HIV-1 RNA Category	**QUAD (N =348)**	**ATR (N = 352)**	**QUAD (N = 353)**	**ATV/r+TVD (N = 355)**
Virologic Success at Week 48[a]				
HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)	316 (89.5%)	308 (86.8%)
Difference in Percentages (95% CI)	3.6% (–1.6% to 8.8%)		3.0% (–1.9% to 7.8%)	
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)	19 (5.4%)	19 (5.4%)
HIV-1 RNA > 50 copies/mL	13 (3.7%)	11 (3.1%)	7 (2.0%)	8 (2.3%)
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)	4 (1.1%)	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[b]	8 (2.3%)	12 (3.4%)	8 (2.3%)	11 (3.1%)
No Virologic Data in Week 48 Window	18 (5.2%)	31 (8.8%)	18 (5.1%)	28 (7.9%)
Discontinued Study Drug Due to AE/Death[c]	10 (2.9%)	19 (5.4%)	11 (3.1%)	18 (5.1%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b]	8 (2.3%)	11 (3.1%)	7 (2.0%)	9 (2.5%)
Missing Data During Window but on Study Drug	0	1 (0.3%)	0	1 (0.3%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; ITT, intent-to-treat; TVD, Truvada

a Week 48 window is between Day 309 and 378 (inclusive).

b Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

c Includes patients who discontinued due to an AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

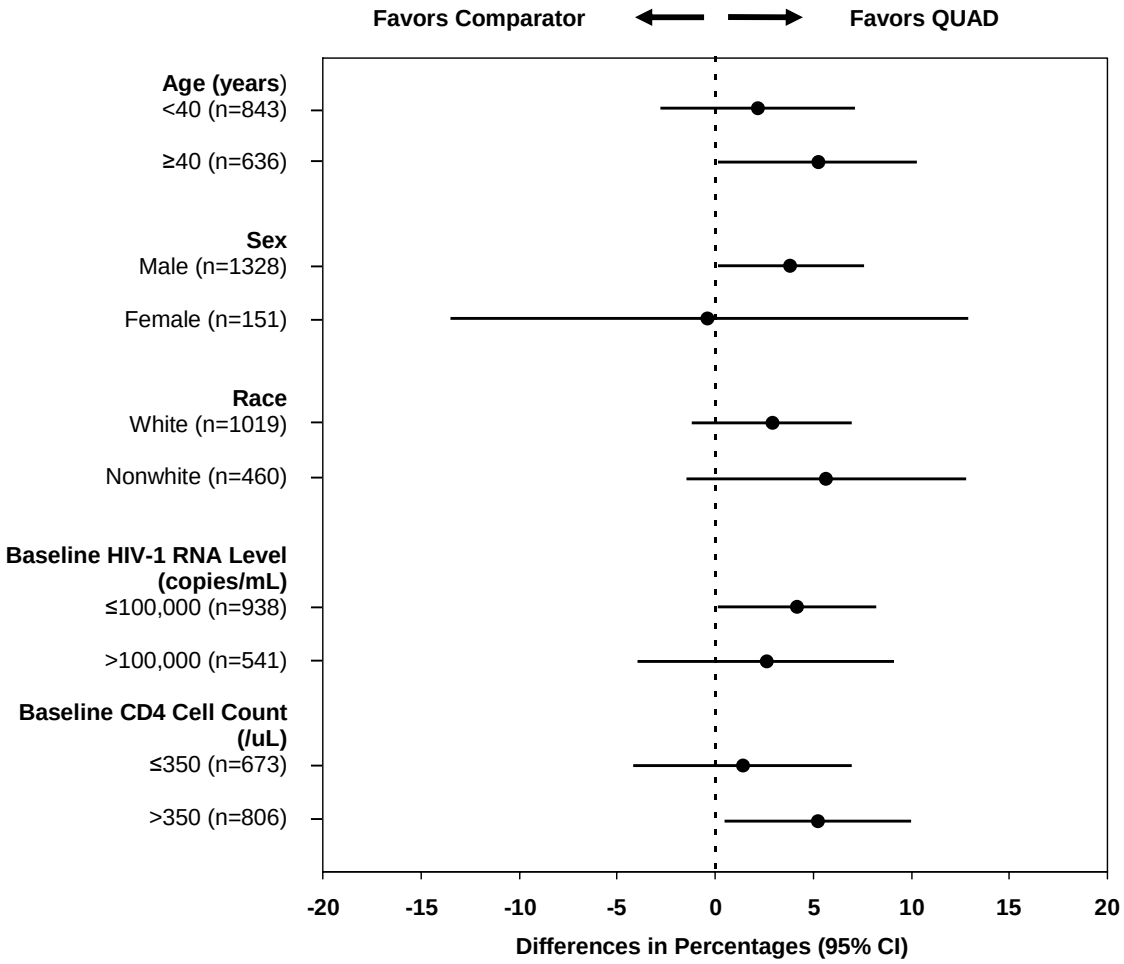
2.7.3. Comparison of Efficacy Results in Subpopulations

The primary analysis of virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis algorithm, ITT analysis set) was analyzed for QUAD versus comparator for age (< 40 and ≥ 40 years), sex, and race (white and nonwhite) in accordance with ICH M4E guidance. Virologic response was also analyzed by baseline HIV-1 RNA level (≤ 100,000 and > 100,000 copies/mL) and baseline CD4 cell counts (≤ 350 and > 350 cells/µL), which are widely accepted surrogate markers of HIV disease severity.

Subgroup analyses revealed high and generally comparable rates of virologic success in the QUAD and control groups with those observed for the overall study population, with point estimates mostly favoring the QUAD group, as seen in the overall population and across various efficacy endpoint analyses. Point estimates for the pooled data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 are presented in Figure 1.

Additional adhoc analyses were performed on Study GS-US-236-0103 on the treatment difference in virologic success by region at Week 48 (GS-US-236-0104 and GS-US-236-0102 were conducted in the US only). In the QUAD group, 92.3% of the non-US subjects and 87.3% of the US subjects had HIV-1 RNA < 50 copies/mL at Week 48. In the ATV/r+TVD group, 90% of the non-US subjects and 83.8% of the US subjects had HIV-1 RNA < 50 copies/mL at Week 48 (Table 16).

Figure 1. **GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis, Pooled ITT Analysis Set)**



CI, confidence interval; ITT, intent-to-treat; MH, Mantel-Haenszel
Note: Difference in response rate and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (if it was not the subgroup factor) and study (for pooled analysis).

2.7.4. Summary of Clinical Resistance Findings

The protease/reverse transcriptase (PR/RT) genotype was assessed for subjects at screening. Resistance analyses were performed on plasma HIV-1 isolates from all subjects with confirmed VF or HIV-1 RNA > 400 copies/mL at Week 48 (Week 60 in Study GS-US-236-0104) or at the time of early study drug discontinuation (ESDD).

In a pooled analysis of antiretroviral treatment-naive subjects receiving the QUAD STR in Phase 2 Study GS-US-236-0104 and Phase 3 Studies GS-US-236-0102 and GS-US-236-0103, the development of 1 or more primary EVG, FTC, or TFV

resistance-associated substitutions was observed in 13 of the 26 subjects with evaluable genotypic data from paired baseline and QUAD treatment-failure isolates (1.7%, 13 of 749 subjects). The most common substitutions that emerged were M184V/I (1.6%, 12 of 749 subjects) and K65R (0.5%, 4 of 749 subjects, all in combination with M184V/I) in reverse transcriptase (RT) and a primary mutation in integrase (1.5%, 11 of 749 subjects) T66I (n = 2), E92Q (n = 8), Q148R (n = 3), and N155H (n = 3) in integrase. Other INSTI mutations (secondary integrase mutations) that developed, each in a single case in addition to a primary INSTI mutation, were H51Y, L68V, G140C, S153A, and E157Q.

Phenotypic resistance data were available for 26 subjects receiving the QUAD STR; 11 of 749 (1.5%) subjects had reduced susceptibility to EVG, 12 of 749 (1.6%) subjects had reduced susceptibility to FTC, and 2 of 749 (0.3%) subjects had reduced susceptibility to TFV. Substantial cross-resistance was observed between EVG and RAL, and between FTC and lamivudine (3TC; Epivir®). These subject isolates remained susceptible to common second-line treatment regimens consisting of PIs, NNRTIs, and most other NRTIs.

In Study GS-US-236-0103, 27 subjects in the QUAD group had the NNRTI-associated K103N substitution in RT at baseline; none of these subjects developed resistance to a component of the QUAD STR. The presence of K103N at baseline did not predispose subjects to failure on the QUAD STR or ATV/r+TVD. No subjects from Study GS-US-236-0102 had K103N, as required by the protocol. In Studies GS-US-236-0102 and GS-US-236-0103, 18 subjects had primary PI-associated resistance mutations at baseline (3 with reduced susceptibility to ATV, but all were susceptible to ATV/r, therefore meeting entry criteria for the study); none of these subjects developed resistance to a component of the QUAD STR.

2.7.5. Safety Data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

The safety and tolerability profile of the QUAD STR for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients is supported by a robust safety database consisting of 749 HIV-1 infected patients with a median duration of exposure to the QUAD STR of 48.4 weeks. The extent of exposure of the QUAD STR in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 is presented in Section 8.2. A brief summary of AEs reported in the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 is provided in Table 19.

The QUAD STR was well tolerated, as demonstrated by the low number of AEs leading to study drug discontinuation (3.5%, 26 of 749 subjects) and also by the fact that most AEs were mild to moderate in severity. There were low overall incidences of treatment-emergent death and serious adverse events (SAEs). The most frequently reported AEs for QUAD were diarrhea, nausea, and headache. Subgroup analyses of AEs by baseline characteristics of sex, age, race, and HIV baseline characteristics of viral load and CD4 cell count showed no clinically meaningful differences between subgroups. Data for EVG in antiretroviral treatment-experienced subjects and for COBI as a booster of ATV in antiretroviral

treatment-naive subjects also support the favorable safety and tolerability profiles of these agents (Section 8.18).

Similar percentages of subjects in the QUAD, Atripla, and ATV/r+TVD groups reported any SAE (QUAD 9.2%, 69 of 749 subjects; Atripla 6.7%, 25 of 375 subjects; ATV/r+TVD 8.7%, 31 of 355 subjects).

Phase 1 Study GS-US-216-0121 showed that COBI administration resulted in a reversible increase in serum creatinine without affecting actual renal glomerular filtration rate as assessed via iohexol clearance (Section 5.1.3.2.2). Serum creatinine is cleared by the kidney through a combination of glomerular filtration and active secretion. Active tubular secretion is a minor component of the clearance of creatinine, accounting for 10% to 40% in patients with normal renal function, with greater variability in patients with chronic kidney disease {11602}, {10070}, {11576}. Similar to other commonly used drugs including cimetidine and trimethoprim {18704}, COBI has been found to be associated with reversible increase in serum creatinine without affecting actual glomerular filtration rate, likely via an inhibition of renal OCT2 and MATE1. As expected based on the results of Study GS-US-216-0121, small increases in serum creatinine, which led to small decreases in eGFR calculated using the Cockcroft-Gault equation ($eGFR_{CG}$), were also observed in subjects who received QUAD in the Phase 3 studies. The changes were noted as early as Week 2 of treatment, with only minimal changes after Week 4. However, no decreases in cystatin C clearance, a marker of glomerular filtration, were observed in these studies. Because the small initial increase in serum creatinine and initial reduction in eGFR is predictable after QUAD initiation, serum creatinine and eGFR are still adequate tests to monitor renal function in patients initiating QUAD.

Six subjects discontinued in the QUAD group (< 1%) and 1 subject discontinued in the ATV/r+TVD group due to renal events (Appendix 5). Of the 6 subjects in the QUAD group:

- 2 subjects had small increases (~0.2 to 0.3 mg/dL) in serum creatinine without tubular dysfunction within weeks of initiation the QUAD STR. For 1 subject, serum creatinine levels returned to baseline after study drug discontinuation, reflecting the effect of COBI on serum creatinine. For the other subject, serum creatinine levels improved but did not return to baseline due to the subject switching to an RTV-boosted PI regimen.

- 2 subjects had rapid increases in serum creatinine with tubular dysfunction within a few weeks of initiation the QUAD STR. For both subjects, renal abnormalities improved or resolved soon after discontinuation of the QUAD STR. Both subjects had either screening or baseline eGFR < 70 mL/min and violated the study protocol because the subjects were not discontinued from QUAD when their eGFR decreased below 50 mL/min (per protocol-defined stopping rules based on prescribing information for FTC and TDF).

- 2 subjects showed slow and gradual increases in serum creatinine with tubular dysfunction over months after initiation with the QUAD STR, which improved after discontinuation of study drug.

Five out of the 6 subjects in the QUAD group had evidence of renal impairment at baseline (GFR < 90 mL/min or at least 1+ proteinuria). The type of renal adverse reactions seen in the QUAD Phase 3 studies have been reported with the use of TDF, as described in labeling for all approved TDF-containing products (ie, Viread, Truvada, Atripla, and Complera). The rate of reported renal AEs leading to discontinuations with the QUAD STR was consistent with the rate reported in studies using an RTV-boosted PI along with a TDF-based background regimen (Section 8.7.1).

In the QUAD safety update data cut (21 November 2011) for Studies GS-US-236-0102 and GS-US-236-0103, an additional subject (b) (6)) discontinued QUAD therapy due to an AE of increased blood creatinine. After discontinuation of QUAD, the subject's laboratory values returned to baseline values (Appendix 5).

Clinically relevant bone abnormalities have not been seen with TDF in long-term (> 3 years) clinical studies in HIV-1 infected adults, and were not seen over 48 weeks in the studies with QUAD. In Study GS-US-236-0103, there were comparable decreases in baseline bone mineral density (BMD) at the lumbar spine and hip in the QUAD group compared with the ATV/r+TVD group (changes at Week 48: spine –2.63% in the QUAD group vs –3.33% in the ATV/r+TVD group; hip –3.06% in the QUAD group vs –3.88% in the ATV/r+TVD group).

The QUAD STR demonstrated a favorable safety profile with clinically relevant tolerability advantages over both Atripla and ATV/r+TVD as follows:

- Treatment-emergent Grade 4 laboratory abnormalities were reported less frequently in the QUAD group than in the Atripla group or the ATV/r+TVD group: QUAD 3.9% of subjects with maximum Grade 4 abnormalities; Atripla 9.7% of subjects with maximum Grade 4 abnormalities; and ATV/r+TVD 15.9% of subjects with maximum Grade 4 abnormalities.

- In the pooled safety analysis set in Studies GS-US-236-0102 and GS-US-236-0103, mean increases from baseline through Week 48 in fasting total cholesterol and LDL cholesterol were lower for the QUAD group compared with the Atripla group. Mean increases from baseline through Week 48 in fasting triglycerides were lower for the QUAD group compared with the ATV/r+TVD group.

- In the pooled safety analysis set in Studies GS-US-236-0104 and GS-US-236-0102, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported a neurological/psychiatric AE based on a prespecified analysis (QUAD 42.9%, 170 subjects; Atripla 62.1%, 233 subjects).

- In the pooled safety analysis set in Studies GS-US-236-0104 and GS-US-236-0102, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported any rash AE based on a prespecified analysis (QUAD 17.5%, 131 subjects; Atripla 27.7%, 104 subjects).

- Lower percentages of subjects in the QUAD group than in the ATV/r+TVD group had graded abnormalities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

- The renal safety profile of QUAD STR is consistent with the known and manageable renal toxicity associated with the use of TDF.

In conclusion, the QUAD STR was well tolerated with a safety profile that compares favorably with those of current US DHHS-preferred NNRTI- and PI-based regimens in HIV-1 infected subjects.

2.7.6. Safety Data for COBI-Containing Studies GS-US-236-0104, GS-US-236-0102, GS-US-236-0103, GS-US-216-0105 and GS-US-216-0114

In addition to the 7 subjects who discontinued QUAD therapy due to renal events, 6 subjects discontinued due to renal events in the COBI-boosted atazanavir (ATV/co)+TVD group in COBI studies GS-US-216-0105 and GS-US-216-0114. Combining the QUAD group from Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 plus the ATV/co+TVD group (n =1143), a total of 13 patients (1%) discontinued a COBI+TDF-containing regimen due to a renal event. Combining the ATV/r+TVD group from QUAD Study GS-US-236-0103 and the ATV/r+TVD group from COBI Studies GS-US-216-0105 and GS-US-216-0114 (n = 732), a total of 7 patients (1%) discontinued due to a renal event. The rate of renal events leading to discontinuation was the same between the TDF regimen with COBI, and the regimen containing TDF with a boosted PI.

Given that approximately 50% of current TDF use is in combination with an RTV-boosted PI, the results of the above pooled analyses are reassuring and help put this infrequent event in context.

2.7.7. Safety Data for GS-US-236-0118

Study GS-US-236-0118 is an ongoing Phase 3 study evaluating the safety of COBI-containing regimens (including the QUAD STR) in HIV-1 infected adults with mild-to-moderate renal impairment (eGFR between 50 and 89 mL/min). Cohort 1 enrolled treatment-naive HIV-1 infected adult subjects with HIV-1 RNA $\geq$ 1000 copies/mL and subjects were treated with the QUAD STR. Cohort 2 enrolled treatment-experienced HIV-1 infected adults with HIV-1 RNA < 50 copies/mL and subjects were treated with ATV/co or COBI-boosted DRV (DRV/co) plus 2 NRTIs.

In the QUAD safety update data cut, there were no SAEs or deaths. One subject from Cohort 2 had an AE that led to discontinuation of study drug; the AE of “affect lability” (reported term: emotional volatility) was reported to have started 2 days after the initiation of study drug and resolved without treatment 2 days after study drug was discontinued. The event was assessed as nonserious and related to study drug by the investigator. In Cohort 1 there was a small increase in median values for serum creatinine (baseline median

1.18 mg/dL; the median change from baseline at Week 8 was 0.11 mg/dL). The observed changes were similar to those seen in the pooled QUAD group in Phase 2 and 3 studies. In Cohort 2, there were no notable changes from baseline through Week 8 in median values for serum creatinine (Section 8.18.3.1).

2.8. Renal Management Recommendations

The renal management recommendations are based on clinical studies with the QUAD STR and COBI. The Phase 3 QUAD and COBI studies required screening $eGFR_{CG} \geq 70$ mL/min in order to avoid potential early discontinuations from study drug resulting from the expected inhibitory effect of COBI on creatinine secretion. Given that QUAD contains FTC and TDF, and that their US prescribing information requires dose adjustment when GFR decreases to < 50 mL/min, and since QUAD is an STR that cannot be dose adjusted, subjects in the Phase 3 QUAD studies with a GFR < 50 mL/min were required, per protocol, to discontinue study drug. This, along with current label recommendations for TDF and for TDF-containing products, forms the basis for the proposed QUAD label recommendations regarding required GFR prior to initiation of therapy.

In an effort to assess renal laboratory findings in the QUAD program independent from investigator-reported AEs, and to better characterize the renal safety of QUAD, we explored confirmed serum creatinine increases of 0.4 mg/dL as a threshold to discriminate the effect of COBI on serum creatinine secretion from TDF renal toxicity. This threshold was derived from the mean change from baseline (0.14 mg/dL) and standard deviation (0.13 mg/dL) in creatinine for subjects receiving QUAD in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103. Using this threshold, we identified subjects with confirmed changes in creatinine that were above the mean + 2 × SD (0.4 mg/dL).

A confirmed serum creatinine increase of ≥ 0.4 mg/dL (using the NDA dataset) occurred in 18 (2.4%) subjects receiving QUAD: 14 (1.9%) subjects continued on study drug without features of tubulopathy, and 4 (0.5%) subjects discontinued study drug due to renal AEs with features of tubulopathy.

Although a confirmed increase in serum creatinine of ≥ 0.4 mg/dL was present in the 4 subjects with renal AEs described above, 14 subjects who experienced the same degree of confirmed creatinine increase were able to continue study drug without any clinical or other laboratory evidence of renal toxicity; their creatinine values also stabilized or improved over time while on study drug. Of the 749 subjects receiving QUAD, 731 did not experience a confirmed serum creatinine increase of ≥ 0.4 mg/dL, and did not develop clinical or other laboratory features of tubulopathy; 2 subjects discontinued study drug due to an AE of serum creatinine elevation attributed to COBI.

Since confirmed changes in serum creatinine ≥ 0.4 mg/dL from baseline in patients receiving QUAD are unlikely to be related to COBI, such a change may indicate an effect attributable to TDF. Patients with serum creatinine changes above this threshold may be at risk of TDF-related renal toxicity and may need to be monitored more frequently.

Increases in markers of tubular injury (glycosuria, proteinuria, and hypophosphatemia) are not expected with COBI, and changes in these laboratory parameters regardless of creatinine levels may herald possible TDF renal toxicity.

Results of the Phase 3 studies showed that COBI's inhibition of creatinine secretion is rapid and near maximal by Week 2, stabilizing by Week 8 to 16 without further declines thereafter. Consistent with the current labeling of TDF-containing products, routine monitoring of creatinine clearance (CL_{cr}) and serum phosphorus should be performed during therapy with QUAD in patients with renal impairment and in patients at risk for renal impairment.

2.9. Overall Benefits and Risks

There remains a need for new therapeutic options for patients infected with HIV-1 that demonstrate potent and sustained efficacy with favorable tolerability and minimal long-term toxicity, combined with practical and convenient dosing regimens. The most significant challenge in achieving long-term virologic suppression is the avoidance of drug resistance. Incomplete or partial adherence to treatment regimens is a critical factor contributing to the development of resistance and treatment failure. Studies have shown that a once-daily STR significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {13840}, {15302}, {15951}, {15415}. The development of STRs is a strategy employed to simplify treatment and improve adherence to therapy in order to achieve better rates of virologic suppression, resulting in improved long-term outcomes in patients with HIV infection.

The QUAD STR combines a novel INSTI, EVG, boosted by COBI, with the standard of care, US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada) in a once-daily tablet. Pending regulatory approval, QUAD would be the first INSTI-based STR for the treatment of HIV-1 infection. The following considerations support a favorable benefit/risk profile for the QUAD STR for the treatment of adult HIV-1 infected adults.

Benefits

- Virologic response rates of 90% and 88% in the two Phase 3 QUAD STR studies were among the highest seen in clinical studies in antiretroviral treatment-naive HIV-1 infected adult subjects
- Demonstrated potent, durable, and rapid antiretroviral activity regardless of baseline viral load and CD4 cell count
- Demonstrated immunologic benefits by increases in CD4 cell count
- Frequency of resistance development in subjects taking the QUAD STR was < 2%
- Preserves use of NNRTI- and PI-based regimens for INSTI failures with resistance
- Achieved virologic suppression in antiretroviral treatment-naive patients with transmitted resistance to NNRTIs (K103N)

- Fewer CNS and rash AEs compared with Atripla
- Lower bilirubin-related AEs compared with ATV/r+TVD
- Overall low rates of treatment-emergent death, SAEs, or study drug discontinuation due to AEs, and treatment-emergent Grade 3 or 4 laboratory abnormalities
- Favorable total cholesterol and LDL profile of the QUAD STR compared with an NNRTI-based regimen
- Lower mean increases from baseline in fasting triglycerides compared with ATV/r+TVD
- Proposed as Pregnancy Category B, as none of the components of the QUAD STR have shown direct or indirect harmful effects with respect to pregnancy and embryonal/fetal development
- Contains the US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada)
- Extensive postmarketing experience with the FTC and TDF individual components of the combination, and also the Truvada combination tablet
- Administered once daily
- Simplification of therapy with the first STR containing an HIV integrase-strand transfer inhibitor

Risks

- Rates and types of renal AEs leading to study drug discontinuation were consistent with published clinical studies and postmarketing data included in labeling for TDF-containing products. In all subjects who discontinued QUAD due to renal AEs, renal laboratory parameters improved.
- While small increases in serum creatinine are expected after initiation of QUAD, they do not represent reduction in actual GFR or renal injury. Serum creatinine is cleared by the kidney through a combination of glomerular filtration and active secretion. Active tubular secretion is a minor component of the clearance of creatinine, accounting for 10% to 40% in patients with normal renal function with greater variability in patients with chronic kidney disease {11602}, {10070}, {11576}. COBI inhibits active secretion of creatinine, thereby leading to small creatinine elevations. COBI does not affect glomerular function (Section 5.1.3.2.2).
- Coadministration with drugs that are highly dependant on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening AEs.

- Coadministration with drugs that strongly induce CYP3A, may lead to lower exposure of EVG and COBI and loss of efficacy of the QUAD STR.

Conclusion

The QUAD STR has demonstrated both potent and durable antiviral efficacy with a safety and tolerability profile that offers an alternative with advantages over the currently recommended first-line NNRTI- and PI-based antiretroviral regimens. The QUAD STR is the first fixed-dose combination containing an HIV integrase strand-transfer inhibitor for use once daily in the treatment of HIV-1 infection. The QUAD STR has a favorable benefit/risk profile and represents a new therapeutic option for HIV-1 infected adults who are antiretroviral treatment-naive or have no known substitutions associated with resistance to the individual components.

3. BACKGROUND

3.1. Rationale for Development of the QUAD STR

3.1.1. Treatment Landscape for HIV-1 Infection in Adults in the US

HIV-1 infection is a serious and life-threatening disease that is of major public health interest in the US. There are approximately 1.1 million people in the US living with HIV-1 (34 million people worldwide) {15971}, {19661}. In the US, approximately 75% of all people diagnosed with HIV are men {19777}. Populations most affected by HIV infections include men who have sex with men (57% of HIV diagnoses), blacks/African Americans (44% of HIV diagnoses), and Hispanics/Latinos (20% of HIV diagnoses) {19776}.

If left untreated or suboptimally treated, the infection is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, and ultimately results in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of HAART; the introduction of HAART was associated with a dramatic decrease in AIDS-related morbidity and mortality {2537}, {5125}, {8284}. With advances in HIV treatments over the last decade, there has been a shift towards initiating treatment earlier to improve overall outcomes. Treatment with antiretrovirals has also been shown to reduce HIV-1 transmission rates {19827}.

The primary goals of antiretroviral therapy for HIV-1 infection are to reduce HIV-associated morbidity, prolong duration and quality of life, restore and preserve immunologic function, maximally and durably suppress plasma HIV-1 viral load, and prevent HIV transmission. The US DHHS Guidelines for Use of antiretroviral Agents in HIV-1 Infected Adults and Adolescents suggest that preferred initial therapy for antiretroviral treatment-naive HIV-1 infected patients consists of 2 NRTIs/NtRTIs and either the NNRTI EFV, 1 of 2 boosted PIs—DRV or ATV—,or the INSTI RAL. The US DHHS guidelines list FTC (Emtriva) and TDF (Viread) as the preferred dual NRTI/NtRTI backbone in an antiretroviral regimen for initial therapy. TDF and FTC, the NRTI components of the QUAD STR, were developed by Gilead and have been approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in the US, the EU, and other markets worldwide. TDF and FTC are also co-formulated as Truvada and both drugs are also part of the STRs Atripla, and Complera for the treatment of HIV-1 infection. The preferred regimens for HIV-1 infected treatment-naive adults suggested in the US DHHS guidelines are outlined in Table 2 {20239}.

Table 2. Preferred Regimens for Antiretroviral Treatment-Naive Patients (US DHHS Guidelines)

Regimen[a] Generic Names	Abbreviation	Brand Name(s)	Daily Number of Tablets/Capsules	Dosing Frequency
NNRTI-Based Regimen				
Efavirenz/tenofovir DF/emtricitabine	EFV/TDF/FTC	Atripla	1	Once Daily
PI-Based Regimens				
Ritonavir-boosted atazanavir + tenofovir DF/emtricitabine	ATV/r + TDF/FTC	Reyataz + Norvir + Truvada	3	Once Daily
Ritonavir-boosted darunavir + tenofovir DF/emtricitabine	DRV/r + TDF/FTC	Prezista[b] + Norvir + Truvada	4	Once Daily
INSTI-Based Regimen				
Raltegravir + tenofovir DF/emtricitabine	RAL + TDF/FTC	Isentress + Truvada[c]	3	Twice Daily

INSTI, integrase strand-transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; US DHHS, United States Department of Health and Human Services

a All regimens contain Truvada as the US DHHS-preferred NRTI/NtRTI backbone.

b Two 400-mg tablets

c Truvada is taken once daily

NNRTIs are widely used in the treatment of HIV-1 infection; however, they have been associated with safety and tolerability concerns such as hepatotoxicity, CNS symptoms, rash, and/or the risk of teratogenicity {20239}.

Advantages of RTV-boosted PI-based regimens include excellent virologic potency and a high barrier for development of drug resistance (ie, requires multiple mutations). However, RTV-boosted PIs may be associated with metabolic complications such as dyslipidemia, lipodystrophy, and insulin resistance and have the potential for multiple drug interactions due to metabolism via hepatic enzymes {19048}, {15873}, {14110}. The use of RTV-boosted PIs is hampered by the additional pill burden, tolerability issues, and potential for off-target activity (ie, effects on enzymes other than CYP3A) with RTV.

RAL is the only INSTI approved for use in adults. It requires twice-daily dosing, a regimen recently confirmed by the early termination of a study (QDMRK study) comparing once-daily with twice-daily RAL use that showed a lower response rate, higher VF, and higher resistance in subjects with viral loads > 100,000 copies/mL when administered once daily {19639}. RAL has fewer drug-related AEs and lipid changes than EFV, does not require boosting, and has fewer drug-drug interactions than other NNRTI- and boosted PI-based regimens {18376}.

High rates of efficacy have been demonstrated with standard-of-care regimens. Historical results from Phase 3 studies of EFV-plus-NRTI-containing regimens in treatment-naive subjects demonstrated virologic responses (HIV-1 RNA < 50 copies/mL) of approximately 80% at Week 48 {17599}. Results from a Phase 3 study of ATV/r-plus-NRTI-containing regimens in treatment-naive subjects demonstrated virologic responses (HIV-1 RNA < 50 copies/mL) of 78% at Week 48 {14695}. Results from a Phase 3 study of RAL in treatment-naive subjects demonstrated virologic responses (HIV-1 RNA < 50 copies/mL) of 86% at Week 48 {14246}.

3.1.2. STRs in the Treatment of HIV-1 Infection

Benefits of STRs

Studies have shown that a once-daily STR (Atripla) significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {13840}, {15302}, {15951}, {15415}. In a study in which subjects taking an initial regimen with multiple pills switched to a simplified single-tablet once-daily regimen, patients had significant improvement in preference of current regimen to their prior regimen (85% at Week 48 compared with 64% at Week 4). In this study, 89% of subjects had ≥ 95% adherence and the vast majority of subjects described their regimen as “very easy to take”: 97% at Week 48 on the STR compared with 81% on their original regimen ($p < 0.0001$) {13840}. In another study, adherence significantly improved from 93.8% to 96.1% ($p < 0.01$) and overall quality of life improved from 68.8% to 72.7% ($p = 0.042$) when subjects’ regimens were substituted with an STR. In this study, the subjects with the lowest percentiles of quality of life also had worse adherence compared with the subjects in the highest percentiles in every way measured: doses in the last month (92.9% vs 98.5%), doses in the last month taken at the correct time (82.6% vs 97.3%), doses taken in the last week (94.8% vs 98.6%), and doses in the last week taken at the correct time (85.2% vs 97.7%) {15951}. In a study in the hardest-to-treat subjects in a homeless population in San Francisco, treatment with an STR resulted in significantly improved adherence (13% difference favoring STR, $p = 0.001$) and improved virologic suppression (23% difference favoring STR, $p = 0.02$) {15415}, {16661}.

In a national data base review of more than 7073 HIV patients with commercial insurance, patients taking an STR were 59% more likely to achieve 95% adherence compared with those taking 3 or more pills per day. In addition, patients who received an STR were 24% less likely to have a hospitalization compared with those who received 3 or more pills per day {20207}. Another study also found that STRs were associated with a 25% reduced risk of hospitalization, a 17% reduction in total healthcare cost including reduced inpatient and outpatient costs, and reduced monthly out-of-pocket pharmacy expenditures {18702}, {18900}.

Limitations of Current STRs

To date, there are 2 STRs (both containing an NNRTI and Truvada) approved for once-daily administration in the treatment of HIV-1 infection: Atripla and Complera.

Atripla contains EFV, which has been associated with CNS symptoms including dizziness, insomnia, impaired concentration, somnolence, abnormal dreams, and hallucinations, which occurred in 53% of subjects compared with 25% in comparator arms in EFV registrational studies. These CNS symptoms led to EFV discontinuation in 2.1% of patients in registrational studies and up to 13% in a retrospective study {18921}, {20251}. EFV has also been associated with new onset skin rashes in 26% of patients compared with 17% in control groups {18921}. The skin rash led to discontinuation of EFV in 1.7% of patients {18921}. In Study ACTG5202, EFV was associated with greater increase in total cholesterol and low-density lipoprotein (LDL) cholesterol compared with ATV/r, regardless of the NRTI backbone (abacavir/lamivudine or FTC/TDF), which has implications for long-term cardiovascular risk {19273}. In addition, EFV is classified as a teratogen (Pregnancy Category D: positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans). The Atripla Prescribing Information states that, “Pregnancy should be avoided in women taking Atripla.” The pregnancy risk occurs in the first trimester and can cause fetal harm before a patient is aware of her pregnancy; therefore Atripla has limited use in women of childbearing potential {18921}.

Complera contains RPV, for which the incidence of both virologic failure and resistance was higher in subjects with high baseline viral load (HIV-1 RNA > 100,000 copies/mL). Complera also must be taken with food, but cannot be taken with proton pump inhibitors {18319}. There are currently no approved STRs that combine either a PI or an INSTI with an NRTI backbone into a once-daily tablet.

The use of NNRTI-based STRs is also limited by the presence of transmitted NNRTI resistance mutations in newly infected patients. Approximately 8% of antiretroviral treatment-naive patients have been shown to harbor NNRTI resistance {20246}.

Therefore, there remains a need for alternative STRs with potent and sustained efficacy with a favorable tolerability and safety profile across the different subgroups (eg, age, sex, race, baseline HIV-1 RNA level, and baseline cluster of differentiation 4 [CD4] cell count) of the HIV-1 infected patient population.

3.1.3. The QUAD STR

Gilead has developed an STR that contains a fixed-dose combination of EVG, COBI, FTC and TDF: the EVG/COBI/FTC/TDF (150/150/200/300 mg) “QUAD” tablet.

EVG is a new chemical entity that belongs to the new class of HIV-1 INSTIs that prevent integration of HIV-1 genetic material into the host-cell genome. EVG specifically inhibits HIV-1 integrase strand-transfer activity and the integration of viral deoxyribonucleic acid (DNA) into host chromosomal DNA in cell culture. It is the second-in-class INSTI (after RAL). Based on its PK and PK/PD results, EVG was developed as a “boosted drug” to enable optimal drug exposure following once-daily administration and hence has robust antiviral activity. The development of EVG as a boosted once-daily drug also made it amenable to coformulation with the US DHHS-preferred dual NRTI/NtRTI backbone of

FTC/TDF (Truvada), which is also administered once daily {20239}. The QUAD STR provided the opportunity for a regimen of 3 potent antiretroviral agents with a favorable PK profile that may be less impacted by late or missed dosing, thus optimizing the possibility of long-term therapeutic success.

RTV is currently used as a booster for PIs, but has properties that limit its use as a pharmacoenhancer for EVG within an STR (Section 3.3). To address these limitations, COBI was specifically designed to be devoid of antiretroviral activity in order to circumvent the theoretical possibility of PI-resistance development when used at low doses as a pharmacoenhancer in the absence of a fully-active PI. Compared with RTV, COBI is a more specific, mechanism-based CYP3A inhibitor with fewer off-target effects on other CYP or UGT metabolizing enzymes. A mechanism-based inhibitor is a substrate for an enzyme that, through the process of its metabolism, generates a metabolite that irreversibly inhibits that enzyme. Mechanism-based inhibition is characterized clinically by evidence of persistent inhibition of enzyme activity after plasma concentrations of the inhibitor have declined {8899}. COBI therefore increases the systemic levels of EVG, whose bioavailability and elimination are affected by metabolism by CYP3A enzymes. Compared with RTV, COBI was also selected to have improved specificity for drug interactions (less/no inhibition of non-CYP3A enzymes; less induction liability), to have improved physicochemical properties to enable coformulation with other antiretrovirals, and to reduce the potential for metabolic side effects due to disruption of lipid metabolism.

FTC is a nucleoside analog of cytidine, and TDF is a prodrug of TFV, a nucleotide analog of adenosine monophosphate. Both have established antiviral activity in combination in vitro studies and in clinical studies. The combination of EVG, FTC, and TFV in 3-drug combination experiments showed synergistic anti-HIV-1 activity. Synergistic anti-HIV-1 activity was maintained in vitro for EVG/FTC/TFV when tested with COBI, showing no unexpected intracellular antagonism.

The principal safety and efficacy studies conducted with the QUAD STR are Phase 2 Study GS-US-236-0104 and Phase 3 Studies GS-US-236-0102 and GS-US-236-0103. The main study designs and population characteristics are summarized in Section 6.1.

The QUAD tablet is the first STR that combines an HIV integrase strand-transfer inhibitor with the US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada). The QUAD STR has demonstrated potent and durable antiretroviral activity (Section 7), a favorable safety and tolerability profile (Section 8), and has the additional benefit of being a complete, once-daily antiretroviral regimen. The safety of TDF and FTC has been well characterized with ~9 and ~4 million patient-years, respectively. The frequency of resistance development in subjects taking the QUAD STR was low (Section 7.2). The QUAD STR is a valuable addition to the current armamentarium of approved antiretrovirals (including the STRs Atripla and Complera, and PI- and RAL-based regimens) for the following reasons:

NNRTI-based regimens:

- Unlike Atripla (Pregnancy Category D), the QUAD STR is proposed as Pregnancy Category B because none of the components have shown direct or indirect harmful effects with respect to pregnancy and embryonal/fetal development in animal studies.

- Unlike Complera, the QUAD STR displayed potent and durable antiviral suppression regardless of baseline viral load.

- In clinical studies, a significantly lower percentage of subjects receiving QUAD compared with subjects receiving Atripla reported any neurological/psychiatric AE (based on a prespecified analysis).

- In clinical studies, significantly lower mean increases from baseline in fasting total cholesterol and LDL were observed in subjects receiving QUAD compared with subjects receiving Atripla.

RTV-boosted PI-based regimens:

- PIs can be associated with metabolic complications such as dyslipidemia, lipodystrophy, and insulin resistance {15873}, {14110}, {19048}. The QUAD STR had lower mean increases from baseline in fasting triglycerides compared with ATV/r+TVD.

- The QUAD STR had lower bilirubin-related AEs compared with ATV/r+TVD.

- The QUAD STR provides treatment-naive patients the opportunity to take a highly effective regimen as a once-daily tablet, whereas the use of PIs is hampered by the additional pill burden associated with the need to coadminister low-dose RTV, and the absence of coformulations with NRTI/N(t)RTI backbones.

RAL-based regimens:

- The QUAD STR is an INSTI-based STR with potent activity and efficacy across low and high viral loads as a once-daily regimen. RAL requires twice-daily dosing, as demonstrated in the QDMRK study comparing once-daily with twice-daily RAL use that showed a lower response rate, higher VF, and higher resistance in subjects with viral loads >100,000 copies/mL when administered once daily {19639}.

- RAL is not available within a fixed-dose combination or STR and has additional pill burden.

3.2. Regulatory History and Proposed Indication Statement

The QUAD STR contains a fixed-dose combination of EVG and COBI and 2 marketed products, FTC and TDF: the EVG/COBI/FTC/TDF (150/150/200/300 mg) tablet.

Truvada is the brand name for the fixed-dose combination film-coated tablet that contains the active substances in Emtriva and Viread. Each Truvada tablet contains Emtriva and Viread at the same dosages as recommended for the individual components, ie, 200 mg of FTC and 245 mg of tenofovir disoproxil (as fumarate, equivalent to 300 mg TDF or 136 mg of TFV). The safety profile of these products has also been well characterized through extensive postmarketing experience (refer to the Truvada prescribing information in Appendix 1). A notable toxicity of TDF is proximal renal tubulopathy, which may warrant treatment discontinuation in a small number of patients (~1%); this is well understood by HIV health-care providers, readily assessed by simple laboratory tests, and reversible upon drug discontinuation (Section 8.7.1).

The efficacy and safety of the marketed products FTC, TDF, and Truvada in combination with other antiretroviral agents for the treatment of HIV-1 infection have been established through comprehensive nonclinical and clinical programs with these medicinal products, as submitted in the original and supplemental NDAs as follows:

- Emtriva 200-mg hard capsules (approved on 02 July 2003) and Emtriva 10-mg/mL oral solution (approved on 28 September 2005)

- Viread 300-mg film-coated tablets (approved on 26 October 2001); Viread 150-, 200-, and 250-mg film-coated tablets and Viread oral powder formulation (approved on 18 January 2012)

- Truvada (Emtriva 200-mg/Viread 300-mg) film-coated tablets (approved on 02 August 2004)

INDs for EVG, COBI, and the QUAD STR were originally submitted on 15 April 2005, 06 March 2008, and 28 July 2008, respectively. As agreed with the FDA, Gilead plans to submit separate NDAs to the FDA for the individual presentations of EVG and COBI in the second quarter of 2012, supported by a Phase 3 study of EVG in treatment-experienced subjects (GS-US-183-0145, Section 8.18.1.1) and a Phase 3 study of COBI as a booster of

ATV in antiretroviral treatment-naive subjects (GS-US-216-0114, Section 8.18.2.2). The development programs and timing of submissions of the NDAs for QUAD, COBI, and EVG were the subject of extensive discussions and agreement with the Division of Antiviral Drug Products at FDA.

The development program for the QUAD STR was granted fast-track designation by the FDA on 01 December 2010. Gilead submitted an NDA for the QUAD STR on 27 October 2011 (NDA 203-100). The principal clinical safety and efficacy data supporting the NDA were derived from one Phase 2 study (GS-US-236-0104) and two Phase 3 studies (GS-US-236-0102 and GS-US-236-0103) conducted with the QUAD STR in antiretroviral treatment-naive, HIV-1 infected adult subjects. The primary endpoint was met in both of the Phase 3 studies, thereby supporting the following proposed indication:

> [TRADENAME] is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment naive or who have no known substitutions associated with resistance to the individual components of [TRADENAME].

Pending regulatory approval, QUAD would be the first INSTI-based STR for the treatment of HIV-1 infection.

3.3. Overview of the Clinical Development Plan for the QUAD STR

The goal of the development plan for the QUAD STR was to provide HIV-1 infected adult patients with the option of taking a once-daily INSTI within an STR containing US DHHS-preferred NRTI/NtRTIs.

EVG is a new chemical entity that belongs to the new class of HIV-1 integrase inhibitors and prevents integration of the HIV-1 genetic material into the host-cell genome. In 2 completed studies (Phase 1 Study GS-US-183-0101 and Phase 2 Study GS-US-183-0105), treatment with EVG resulted in substantial reduction of HIV-1 viral load in HIV-1-infected subjects, with analyses of exposure-response data indicating that a 150-mg dose of EVG/r provides exposures with substantial antiviral activity. The PK/PD relationships of EVG antiviral activity/efficacy leading to dose selection were investigated in the proof-of-concept monotherapy study (GS-US-183-0101) and as a part of an antiretroviral regimen in treatment-experienced HIV-1 infected subjects in a Phase 2 study (GS-US-183-0105). As monotherapy, EVG exhibited PK and PD that supported once-daily dosing in the boosted state (100 mg of the PI RTV) with high trough concentrations, which were best associated with antiviral activity. Based on these PK/PD results, the decision was made to develop EVG as a “boosted drug” and identify a once-daily dose that would be associated with a robust antiviral response, amenable to coformulation, would provide PK compatibility with partner NRTIs, and would be less impacted by late or missed dosing. Additional studies were performed using RTV to “boost” EVG.

Up to 40% of investigational drugs fail to reach the market due to their undesirable PK profile, often due to rapid metabolism by CYP3A {12563}. For many approved drugs, CYP3A metabolism results in inconvenient dosing regimens, large pill burden, high doses,

and unfavorable side effects. RTV, an HIV-1 PI, is an extremely efficient mechanism-based inhibitor of CYP3A that results in significant boosting of CYP3A substrates, including EVG and the HIV-1 PI ATV (which are both coadministered once-daily with RTV 100 mg) {9320}. Liabilities of low-dose RTV include the following: GI AEs that are problematic for some patients even at lower boosting doses; the potential for metabolic complications, including elevations in serum cholesterol and triglycerides; and insulin resistance in some patients {11025}. In addition, low-dose RTV has the potential to select for PI-resistant virus when used as a pharmacoenhancer of EVG in the absence of a fully-active PI.

Because of the limitations of RTV, Gilead developed a new chemical entity, COBI, to boost EVG as part of the QUAD STR. COBI lacks anti-HIV-1 activity, may have fewer adverse effects than RTV (eg, effect on adipocyte functions such as lipid accumulation), and can be coformulated as a tablet with other antiretroviral agents that require boosting. Therefore, Gilead coformulated COBI with EVG, FTC, and TDF into a fixed-dose combination tablet (the QUAD STR). FTC and TDF are nucleoside/nucleotide inhibitors of HIV-1 RT that are currently marketed as separate agents (Emtriva and Viread), as a dual fixed-dose combination (Truvada), and within a triple fixed-dose combination (Atripla).

COBI is a more specific, mechanism-based CYP3A inhibitor than RTV that enhances or "boosts" the exposure of CYP3A substrates, including EVG. In the first-in-human COBI study (GS-US-216-0101), doses up to 200 mg once-daily were well tolerated, with favorable PK and PD, as shown by its ability to reduce the first-pass metabolism and clearance of the CYP3A substrate MDZ to levels similar to that achieved by RTV in healthy subjects.

Gilead conducted Phase 1 and 2 studies to support the use of COBI as a "booster" for EVG, and to characterize the PK and safety of all the components following administration of the QUAD STR. An extensive clinical development program, including one Phase 2 study (GS-US-236-0104) and 2 adequate and well-controlled Phase 3 studies (GS-US-236-0102 and GS-US-236-0103), was conducted with the QUAD STR. Overall, 749 HIV-1 infected subjects were exposed to the QUAD STR in the randomized phases of the Phase 2 and 3 studies.

Gilead is also developing the EVG tablet for use with an RTV-boosted PI and other antiretroviral agents in treatment-experienced adults with HIV-1 infection, and the COBI tablet as a pharmacoenhancer of the HIV-1 PIs ATV and DRV. To date, across the QUAD STR, COBI tablets, and EVG tablets development programs, a total of approximately 1800 and 2600 adult subjects were exposed to COBI and EVG, respectively, either as single agent or as part of the QUAD STR. A total of 898 subjects received the QUAD STR (126 subjects in Phase 1 studies and 772 subjects in Phase 2 or 3 studies), 958 subjects received COBI tablets (564 subjects in Phase 1 studies and 394 subjects in Phase 2 or 3 studies), and 1693 subjects received EVG tablets (1064 subjects in Phase 1 studies and 629 subjects in Phase 2 or 3 studies) (Table 3).

Table 3. Exposure to QUAD, COBI, and EVG Across Development Programs

	Subject Administered QUAD Tablets	Subject Administered COBI Tablets	Subject Administered EVG Tablets
Phase 1 Studies	126	564	1064
Phase 2/3 Studies	772	394	629
All	898	958	1693
		Subjects Exposed to COBI (QUAD or COBI)	**Subjects Exposed to EVG (QUAD or EVG)**
Phase 1 Studies		690	1190
Phase 2/3 Studies		1166	1401
All		1856	2591

4. NONCLINICAL DEVELOPMENT PROGRAM

Comprehensive nonclinical pharmacology/virology, PK, and toxicology programs were undertaken in support of the registration of FTC and TDF. The results of these evaluations were presented in detail in the original NDA and submissions for Emtriva, Viread, and Truvada. Nonclinical data for FTC and TDF are presented in their respective US prescribing information (Emtriva: {12644}, Viread: {16282}, and Truvada: Appendix 1) and are briefly summarized below.

All nonclinical studies that are required to support long-term use of EVG and COBI have been performed as part of the safety assessment of these novel agents. These included the following: a comprehensive set of primary and secondary PD studies; a complete core battery of safety pharmacology studies; a complete PK evaluation; single- and repeat-dose oral toxicity studies in rats and dogs; genotoxicity studies; carcinogenicity studies; assessment of fertility, early embryonic development, pre- and postnatal development, and juvenile toxicity; evaluation of antigenicity, immunotoxicity, phototoxicity, and skin and eye irritation; and qualification of impurities. Studies were also conducted using the combination of EVG and COBI, and EVG and RTV.

All of the definitive safety pharmacology, toxicology, and toxicokinetic studies for EVG, COBI, FTC, and TDF were conducted in accordance with guidelines issued by the ICH and with Good Laboratory Practice (GLP) or other applicable regulations promulgated by international health authorities.

4.1. Summary of Relevant Nonclinical Pharmacology

The overall program, including the data from the combination and individual agent studies, is considered adequate to support the efficacy and safety of the QUAD STR based on the considerations summarized below.

4.1.1. Antiviral Activity and Resistance

The HIV-1 INSTI EVG has potent antiretroviral activity against wild-type laboratory and clinical isolates of HIV-1, against HIV-1 B or non-B subtypes, and against HIV-1 with drug resistance mutations of the NNRTI, NRTI, and PI classes. The HIV-1 NRTIs FTC and TFV, have potent antiretroviral activity against wild-type laboratory and clinical isolates of HIV-1, against HIV-1 B or non-B subtypes, and against HIV-1 with drug resistance mutations of the NNRTI and PI classes, and to some isolates with NRTI resistance mutations. TDF and FTC also have anti-HBV activity. In addition, the combination of EVG, FTC, and TFV in 3-drug combination experiments showed synergistic anti-HIV-1 activity. Synergistic anti-HIV-1 activity was maintained in vitro for EVG/FTC/TFV when tested with COBI, showing no unexpected intracellular antagonism.

The antiviral activity of EVG against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cells, monocyte/macrophage cells, and peripheral blood lymphocytes. EC_{50} values were in the range of 0.02 to 1.7 nM. EVG displayed antiviral activity in cell

culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.1 to 1.3 nM) and HIV-2 (EC_{50} of 0.53 nM). EVG retains potent antiviral activity against HIV-1 with drug resistance mutations of the NNRTI, NRTI, and PI classes. EVG did not show inhibition of replication of HBV or HCV in vitro.

COBI has no detectable antiviral activity against HIV-1, HBV, or HCV and does not antagonize the antiviral effects of EVG, FTC, or TFV.

HIV-1 isolates with reduced susceptibility to EVG have been selected in cell culture as part of the routine development of this inhibitor. Reduced susceptibility to EVG was most commonly associated with the primary integrase substitutions T66I, E92Q, and Q148R. Additional integrase substitutions observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K. As expected based on the structural and mechanistic similarities of EVG and RAL, EVG showed cross-resistance in vitro to the RAL-selected mutations T66A/K, Q148H/K, and N155H.

No in vitro resistance can be demonstrated with COBI due to its lack of antiviral activity.

4.1.2. Safety Pharmacology

In safety pharmacology studies, EVG showed no unwanted pharmacological effects on the central nervous, cardiovascular, respiratory, GI, or renal/urinary systems. Similarly, FTC and TDF had little effect on vital organ systems in safety pharmacology studies.

In vitro patch clamp studies indicated that COBI inhibited the hERG potassium current (IC_{50} 1.8 µM) and the $hCa_v1.2$ L-type calcium channel (IC_{50} 6 µM), but was a weak inhibitor of the $hNa_v1.5$ sodium channel (IC_{50} 86.5 µM). In rabbit Purkinje fibers (protein-free environment), COBI caused a shortening of the APD at ≥ 1 µM; there was no evidence of triangulation, instability, or alternans predictive of prolongation of the QT interval. In 2 Langendorff studies with isolated rabbit hearts (protein-free environment), negative inotropic effects (PR interval prolongation, decreases in LV function) and a shortening of the APD was noted at ≥ 1 µM. The second Langendorff study, with COBI and ATV in combination, was conducted to evaluate the potential for additive effects on the PR interval, as ATV is associated with PR prolongation in humans. When hearts were exposed to COBI in combination with ATV, effects on PR interval and LV function were similar to the decreases noted with COBI alone. COBI had no notable effects, alone or in combination with ATV, on QRS and QT intervals, monophasic APD (MAPD), or triangulation; there were no early after-depolarizations (EADs).

These effects, along with findings from a cardiovascular study in conscious telemetered dogs and ECG evaluations in repeat-dose toxicity studies in dogs up to 39 weeks, suggest that COBI has a low potential for QT prolongation, but may have a tendency to slightly prolong the PR interval, which may be a consequence of interaction with cardiac calcium channels {11876}, {11873}. However, the thorough QT clinical study conducted with COBI doses/exposures (AUC_{tau}) ~2- or 4-fold above therapeutic dose/exposures (GS-US-216-0107), and ECGs and ECHOs conducted during clinical development did not

reveal clinically-significant changes in these parameters. Given the lack of effects for EVG, FTC, and TDF on the cardiovascular system, and the lack of clinical findings with COBI, the potential for cardiovascular effects with the QUAD STR is considered low.

4.2. Summary of Relevant Pharmacokinetics and Drug Interactions

For both EVG and COBI, parent compound is the major circulating component in humans. EVG is primarily eliminated by oxidative metabolism by CYP3A (the major route) and by glucuronidation (minor route) by UGT1A1 and 1A3. When administered with a CYP3A inhibitor, such as COBI, the clearance of EVG is greatly reduced. In other species, EVG is also metabolized via a combination of oxidation and glucuronidation.

COBI is a structural analog of RTV and, like RTV, is a potent mechanism-based inhibitor of human CYP3A enzymes. Detailed in vitro enzyme inhibition studies show similar enzyme inactivation kinetics for the 2 compounds (k_{inact} values of 0.47 and 0.23 min^{-1} and K_I values of 1.1 and 0.26 µM, for COBI and RTV, respectively). Neither compound inactivates nonhuman CYP3A enzymes appreciably, but both compounds are potent reversible inhibitors of CYP3A in all species.

Compared with RTV, COBI shows better specificity as a CYP3A inhibitor, with weak inhibition of 2B6 and 2D6, and no significant inhibition of CYP2C8, CYP2D6, UGT1A1, CYP1A2, CYP2C9, or CYP2C19 activities (Table 4). A clinical study using probe substrates demonstrated no relevant effects on CYP2B6 and weak inhibition of CYP2D6.

Table 4. Comparison of Inhibitory Potencies of COBI and RTV against Human Drug Metabolizing Enzymes

Enzyme	Activity	Calculated IC_{50} (µM)	
		COBI	RTV
CYP1A2	Ethoxyresorufin O-deethylase	> 25	> 25
CYP2B6	Bupropion 4-hydroxylase	2.8	2.9
CYP2C8	Paclitaxel 6α-hydroxylase	30.1	5.5
CYP2C9	Tolbutamide hydroxylase	> 25	3.9
CYP2C19	(S) Mephenytoin 4'-hydroxylase	> 25	> 25
CYP2D6	Dextromethorphan O-demethylase	9.2	3.4
CYP3A	Midazolam 1'-hydroxylase	0.15[a]	0.10[a]
	Testosterone 6β-hydroxylase	0.15[a]	0.11[a]
UGT1A1	β-Estradiol-3-glucuronidation	16.3	4.73

COBI, cobicistat; CYP, cytochrome P450 enzymes; IC_{50}, concentration that results in 50% inhibition; RTV, ritonavir; UGT, uridine diphosphate glucuronosyltransferase

a Representative values (no preincubation step).

COBI and RTV have a similar profile in terms of their interactions with transporters. COBI and RTV are both weak inhibitors of Pgp and BCRP, and moderate inhibitors of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, which are transporters expressed in the intestine and/or liver (Table 5). Clinical studies have demonstrated transient increases in the systemic exposures of representative Pgp and OATP1B1/3 substrates.

Table 5. Inhibition of Transporters Expressed in the Intestine and Liver by COBI and RTV

	IC_{50} (µM)[a]			
	BCRP	**OATP1B1**	**OATP1B3**	**Pgp**
COBI	59	3.50	1.88	36
RTV	> 20	2.05	1.83	> 20

BCRP, breast cancer resistance protein; COBI, cobicistat; IC_{50}, concentration that results in 50% inhibition; OATP, organic anion transporting polypeptide; Pgp, P-glycoprotein; RTV, ritonavir

a Inhibition constants determined using the model substrates Hoechst 33342 and calcein AM for BCRP and Pgp, respectively, and Fluo 3 for OATP1B1 and OATP1B3. Highest concentrations tested for RTV (20 µM) reflects the aqueous solubility limit {18704}.

In the kidney proximal tubule, COBI and RTV are moderate inhibitors of the transporters involved in the active tubular secretion of organic cations, such as creatinine, including OCT2, MATE1, and MATE2-K (Table 6). Notably, COBI shows little or no inhibition for transporters involved in the active tubular secretion of organic anions like TFV, including the organic anion transporter (OAT) 1, OAT3, and MRP4.

Table 6. Inhibition of Transporters Expressed in the Kidney by COBI and RTV

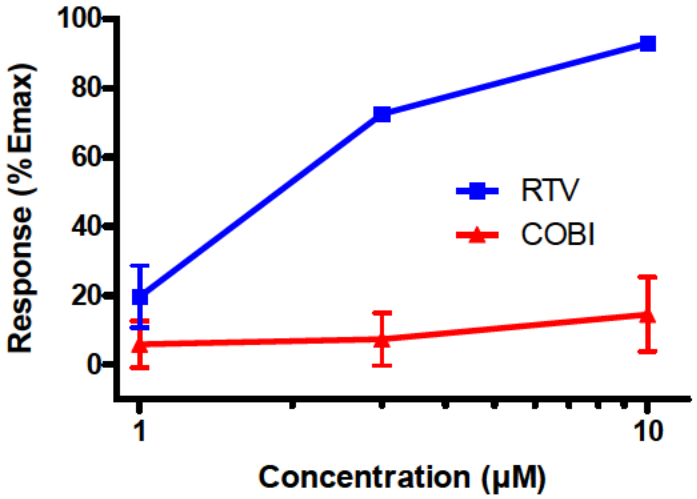
	IC_{50} (µM)[a]						
	Anionic Transporters				**Cationic Transporters**		
	OAT1	**OAT3**	**MRP2**	**MRP4**	**MATE1**	**MATE2-K**	**OCT2**
COBI	> 100	> 100	71	20.7	1.87	33.5	14
RTV	> 20	8.46	> 20	> 20	1.34	> 20	~20

COBI, cobicistat; IC_{50}, concentration that results in 50% inhibition; MATE, multidrug and toxin extrusion protein; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OCT, organic cation transporter; Pgp, P-glycoprotein; RTV, ritonavir

a Inhibition constants for the anionic transporters determined using the model substrates para-aminohippuric acid, estrone-3-sulfate, calcein, and dehydroepiandrosterone-sulfate for OAT1, OAT3, MRP2, and MRP4, respectively. Inhibition constants for all cationic transporters determined using tetraethylammomiun as a model substrate. Highest concentrations tested for COBI (100 µM) and RTV (20 µM) reflect aqueous solubility limits {18704}.

EVG is a weak inducer of CYP3A in vitro, likely through activation of PXR. However, in vivo, increased CYP3A activity is masked by the inhibitory effect of COBI. The expression of other less sensitive PXR targets may be upregulated modestly by EVG. EVG had no effect on the expression of CYP1A2 (controlled by the aryl hydrocarbon receptor). COBI is not expected to be a clinically relevant inducer. In a human hepatocyte study (3 donors) messenger RNA (mRNA) for CYP1A2 and CYP2B6 (controlled by the constitutive androstane receptor) were largely unaffected by treatment with COBI at concentrations up to 30 µM. CYP3A4 mRNA and CYP3A immunodetectable protein (controlled by PXR) were weakly induced, but CYP3A activity remained low, likely due to persistent inhibition. In contrast to COBI, RTV is a potent activator of human PXR, as demonstrated by transactivation studies in vitro (Figure 2) {18810}. It should also be noted that COBI is a potent activator of rat PXR, and rodent toxicology studies showed marked induction of CYP3A and related proteins.

Figure 2. Human PXR Activation by COBI and RTV



COBI, cobicistat; E_{max}, maximum effect; PXR, pregnane X receptor; RTV, ritonavir; SD, standard deviation
Values are mean ± SD (n = 6) for activation in comparison to the strong positive control (10 µM rifampicin).

FTC and TFV are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. The mechanism of active tubular secretion of TFV involves uptake from the blood mediated by OAT1 and OAT3 and efflux into the urine by MRP4 {9318}. In vitro studies and clinical PK drug-drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC and TFV with other medicinal products is low.

4.3. Summary of Relevant Nonclinical Toxicology Results

4.3.1. EVG

The toxicology profile of EVG is well characterized in multiple animal species. The complete nonclinical program included the following: single-dose oral toxicity studies in rats and dogs; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 39 weeks); genotoxicity tests both in vitro and in vivo; 2-year oral carcinogenicity studies in mice and rats; and a full developmental and reproductive toxicity program.

For EVG, no clinically relevant adverse effects were observed in the general toxicity, genotoxicity, carcinogenicity, reproductive, juvenile toxicity, local tolerance, or immunotoxicity studies, or in special mechanistic studies to investigate potential quinolone-related toxicity. Lipid vacuoles, primarily in the lamina propria of the upper small intestine, were observed in repeat oral dose studies in rats and dogs, but were not associated with any adverse consequences and did not progress in long-term studies, and were slowly reversible. Changes in the cecum (increased weights and/or dilatation) were considered to be due to the antibacterial activity of high concentrations of EVG.

In the carcinogenicity studies with EVG, no drug-related increases in tumor incidence were found in mice at doses up to 2000 mg/kg/day (2.4- to 3.8-fold higher than the human systemic exposure at the therapeutic dose of 150 mg/day) or in rats at doses up to 2000 mg/kg/day (12- to 27-fold higher than the human systemic exposure at the therapeutic dose). In the mouse study, high-dose EVG (2000 mg/kg/day) was also administered in combination with RTV (25 mg/kg/day), as it had been previously observed that the addition of RTV, a CYP3A inhibitor, substantially increased the exposure of EVG in mice. No drug-related increases in tumor incidence were noted in these animals at exposures approximately 14-fold higher than the human systemic exposure achieved at the therapeutic EVG dose.

No clinically-relevant target-organ toxicity was observed in single- or repeat-dose nonclinical studies with EVG. The no observed adverse effect levels (NOAELs) are considered to be 2000 mg/kg/day for mice and rats, and 100 mg/kg/day for dogs—the highest doses evaluated in the 13-week, 6-month, and 9-month repeat-dose studies in mice, rats, and dogs, respectively. The combination of 1000 mg/kg/day EVG with 30 mg/kg/day COBI or with 10 mg/kg/day RTV, administered to rats for 90 days, did not result in any notable toxicity findings. Estimated safety margins, based on exposure after repeat dosing (AUC_{0-t}) from the 13-week mouse, 6-month rat, and 9-month dog studies with EVG were 2-fold in mice, at least 20-fold in rats, and over 2-fold in dogs above estimated exposure at the efficacious 150-mg dose in humans.

4.3.2. COBI

The toxicology profile of COBI is well characterized in multiple animal species. The complete nonclinical program included the following: single-dose oral toxicity studies in rats

and dogs; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 39 weeks); genotoxicity tests both in vitro and in vivo; 2-year oral carcinogenicity studies in mice and rats; and a full developmental and reproductive toxicity program.

COBI was not mutagenic or clastogenic in conventional genotoxicity assays. Animal studies did not indicate direct or indirect harmful effects of COBI with respect to pregnancy, embryonal/fetal development, parturition, postnatal development, or fertility.

In repeat-dose studies with COBI, target organs identified were liver (mouse, rat, and dog) and thyroid (rat). The liver effects in mice and rats are considered adaptive changes, are commonly seen in rodents with microsomal enzyme inducers, and are considered secondary to microsomal enzyme induction {17078}, {18407}. COBI induces hepatic CYP3A activity in mice and rats, likely due to species-specific activation of rodent PXR. In dogs, the liver effect (hepatocellular hypertrophy) observed in the 39-week study was considered an adaptive response, and not adverse based on its minimal severity, the absence of degeneration, and its reversibility after cessation of dosing {17078}, {18407}. The thyroid changes in rats are considered adaptive changes, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance {11923}, {11925}, {11927}, {11931}, {11926}, {11933}. The thyroid effects are considered rodent specific and predispose rats, but not humans, to thyroid neoplasms.

Urinalysis changes, noted primarily in high-dose rats (100 mg/kg/day) and dogs (≥ 30 mg/kg/day), included higher urine volume, lower urine specific gravity, and increases in electrolyte excretion. These changes showed no progression after long-term dosing, were reversible, were not associated with remarkable serum clinical chemistry changes—including serum creatinine and blood urea nitrogen (BUN)—and were not associated with any evidence of kidney damage.

Results from a rat immunotoxicity study showed immunosuppressive effects (reduced T-cell dependent antibody response) in females at ≥ 50 mg/kg/day. The no observed effect level (NOEL) in this study was 20 mg/kg/day. In standard 26-week rat and 39-week dog toxicity studies, no microscopic changes suggestive of immunotoxicity were observed in lymphoid organs and immunophenotyping of peripheral blood cells did not reveal any adverse effects at doses up to 100 mg/kg/day in rats and 20 mg/kg/day in dogs. No adverse effects on hematological parameters or IgG levels that could be indicative of immunosuppression, and no increased incidence of infections, have been observed in clinical studies conducted to date with COBI or the QUAD STR (Section 8.14).

In a long-term carcinogenicity study with COBI in mice, no drug-related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). COBI exposures at these doses were 9 (male) and 21 (females) times, respectively, the human systemic exposure at the 150-mg therapeutic dose. In a long-term carcinogenicity study of COBI in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat specific, secondary to hepatic microsomal enzyme induction and thyroid hormone

imbalance, and are not relevant for humans. These epigenetic effects are not relevant for humans because, unlike rats, there is no association between liver enzyme induction and carcinogenesis. Several approved HIV products produce a similar pattern of neoplastic changes in the rodent thyroid, including ritonavir, lopinavir/ritonavir (LPV/r), atazanavir, darunavir, fosamprenavir, nelfinavir, nevirapine, and tipranavir {11931}, {11926}, {11923}, {13467}. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2.6 times the human systemic exposure at the therapeutic dose.

Thirteen-week combination toxicity studies in rats indicate that administration of COBI with EVG or with ATV is unlikely to exacerbate the known toxicities of the individual agents, or lead to unexpected toxicities.

Estimated safety margins, based on exposure after repeat dosing (AUC_{0-t}) from the 13-week mouse, 6-month rat, and 9-month dog studies with COBI were approximately 0.1- to 7-fold (mice), 1- to 2-fold (rats), and 2-fold (dogs) above the estimated exposure at the efficacious 150-mg dose in humans. While the safety margins are not large, effects above the NOAELs were minimal and some effects were species specific. At higher doses than the NOAEL in male mice, liver changes (transaminase elevations and minimal hepatocellular hypertrophy) were observed; female mice were notably less sensitive. In rats, notable effects were limited to decreased body weight gain and food consumption, with slight changes in hematology, clinical chemistry, and urinalysis parameters, and adaptive liver and thyroid changes. In dogs, salivation and emesis, decreased body weight gain and food consumption, slight changes in some clinical chemistry parameters, and minimal adaptive changes in the liver were noted at doses higher than the NOAEL.

4.3.3. Nonclinical Toxicology Conclusions for QUAD

The toxicity profiles of the 4 agents differ substantially with no clinically significant overlapping toxicity. For EVG, increases in cecal weights and/or its contents, likely due to weak antibacterial activity, and lipid-like vacuoles in the upper small intestine were associated with high local concentrations and are not considered relevant to clinical use. The only toxicity observed in chronic animal studies with FTC was mild, reversible anemia in mice and minor decreases in erythrocyte counts/increases in mean corpuscular hemoglobin in monkeys at large multiples of clinical exposure (168-fold in mice; 26-fold in monkeys); therefore, these hematological findings are not considered relevant to clinical use. Potential toxicities related to COBI observed in nonclinical toxicology studies (hematology, clinical chemistry, urinalysis changes, reduced T-cell dependent antibody response in rodents, and adaptive liver and thyroid changes) have not been observed in clinical studies with the QUAD STR. The principal target organs of toxicity in animals following oral administration of TDF were the kidney (karyomegaly, tubular degeneration), bone, and GI tract (in rodents). These findings correlate with the known clinical toxicities for TDF (renal and bone toxicity).

Combination toxicity studies with EVG and COBI, and FTC and TDF did not reveal any new or additive toxicities.

Although COBI was associated with urinalysis changes at high doses in rats and dogs, these changes were reversible, were not associated with remarkable clinical chemistry changes-including serum creatinine and BUN—and were without morphological evidence of kidney damage. COBI is an inhibitor of OCTN1 and MATE1, with similar potencies being found for RTV. These data, along with the clinical data suggest that COBI reversibly blocks secretion of creatinine in humans. Further, given that there is no apparent pathological change in the kidney due to COBI, the routes of excretion differ for TFV and COBI, and that COBI would not be expected to inhibit the major renal transporters of TFV at clinically relevant concentrations, it is not anticipated that the combination of EVG/COBI/FTC/TDF could exacerbate the renal toxicity of TDF.

Gastrointestinal toxicity is dose limiting in rodents for TDF, and was due to high local concentrations. For EVG, changes in the cecum and upper small intestine in rats and dogs were due to high local concentrations and were not considered adverse. These effects are not considered relevant for humans and should not cause an overlapping toxicity with COBI (which caused emesis and salivation in dogs).

COBI, EVG, and FTC have not shown any potential for bone toxicity in chronic rat and dog toxicity studies; thus, exacerbation of any TDF effects on bone is not expected.

NRTIs carry a class labeling for mitochondrial toxicity; however, both FTC and TDF have shown a low potential for mitochondrial toxicity in in vitro studies and long-term toxicity studies. In an in vitro study, EVG showed no inhibitory effects on mitochondrial DNA, suggesting a low potential for mitochondrial toxicity. Accordingly, the potential for mitochondrial toxicity is low when all 4 agents are coadministered.

Of the 4 compounds, only TDF had positive findings in genotoxicity studies. Although EVG showed an equivocal effect in 1 in vitro study, 2 in vivo studies were negative; therefore EVG is unlikely to have the potential to induce chromosome aberrations in vivo. The combination of FTC and TDF in a mouse lymphoma cell assay did not exacerbate the genotoxic potential of TDF. The EVG/COBI/FTC/TDF combination is not anticipated to alter the genotoxicity profiles of the individual agents.

EVG, COBI, FTC, and TDF have all demonstrated low carcinogenic potential in conventional 2-year bioassays. It is considered unlikely that combination dosing would change these profiles, and no exacerbation of toxicity is expected.

EVG, COBI, FTC, and TDF have not shown significant adverse effects in reproductive and developmental toxicity studies, and the combination of the 4 components is not expected to have an altered reproductive toxicity profile compared with that of the individual agents.

The absence of nonclinical safety studies with the 4-drug combination is in accordance with FDA Guidance for Industry, Nonclinical Safety Evaluation of Drug or Biologic Combinations, March 2006. There are no anticipated clinically relevant PK or toxicological interactions expected in the QUAD STR beyond the anticipated PK boosting of EVG by COBI. Further, extensive clinical safety data are available for the approved drugs FTC, TDF, and the FTC/TDF fixed-dose combination product, Truvada.

The nonclinical profile of the individual agents, the lack of overlapping toxicity in animals, along with clinical data with EVG, COBI, and the QUAD STR support the overall benefit/risk profile of this INSTI-based STR for HIV-1 infection.

5. CLINICAL PHARMACOLOGY

Data on the clinical pharmacology data for FTC and TDF are presented in their respective US prescribing information (Emtriva: {12644}, Viread: {16282}, and Truvada: Appendix 1) and will not be discussed in detail in this document.

5.1.1. Dose Selection and Relative Bioavailability

The NRTI components of the QUAD STR, TDF and FTC, were developed by Gilead and have been approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in the US, the EU, and other markets worldwide. Both drugs are also part of Truvada, Atripla, and Complera for the treatment of HIV-1 infection. Each QUAD tablet contains FTC and TDF at the same dosages recommended for the individual components and in other fixed-dose combination products in adults, ie, 200 mg of FTC and 300 mg of TDF. FTC and TDF have been administered as individual agents or in combination (Truvada) as the NRTI backbone in Phase 3 studies with a wide range of antiretrovirals, including EFV, DRV/r, ATV/r, LPV/r, saquinavir/r, RPV, and RAL. As such, the exposure/safety profile of TFV in the setting of RTV-boosted PIs has been well established.

The pharmacokinetics of EVG have been evaluated in the absence and presence of boosting. Boosting of EVG results in significantly increased systemic EVG exposures; in particular, high trough concentrations, and longer median elimination half-life ($T_{1/2}$) (~9 hours boosted vs ~3 hours unboosted) are observed.

The exposure-response relationship of EVG, the third antiretroviral component of the QUAD STR, was evaluated in detail in dose-ranging studies of short-term monotherapy using unboosted and RTV-boosted EVG doses (GS-US-183-0101) and boosted as a part of an antiretroviral regimen (Phase 2 Study GS-US-183-0105) in treatment-experienced subjects, providing a wide range (~20-fold) of EVG C_{trough}, the parameter that best predicts antiviral activity. These analyses demonstrated that boosted-EVG 150 mg exposures were safe, well tolerated, and provided exposures that provided the desired, near-maximal antiviral activity.

The pharmacokinetics of COBI have been evaluated over a dose range of 50 to 400 mg. Consistent with a mechanism-based inhibitor (e.g., ritonavir), COBI displays dose- and time-dependent pharmacokinetics, and provides sustained CYP3A inhibition despite a short plasma half-life (~3 hours). The 150-mg dose of COBI was selected based on dose-ranging studies demonstrating substantial boosting of the validated CYP3A probe substrate MDZ by COBI (GS-US-216-0101) and comparable EVG boosting/exposures in the QUAD STR versus EVG 150 mg boosted with RTV, providing EVG C_{trough} that results in high (~10-fold) inhibitory quotient (IQ) (C_{trough}/IC_{95}: IQ_{95}, protein-binding adjusted) values (GS-US-236-0101). A 100-mg dose of COBI in the QUAD STR provided bioequivalent EVG exposure as assessed by AUC_{tau} and C_{max}, but 37% lower C_{trough}.

The proposed commercial formulation of QUAD used in Phase 3 studies GS-US-236-0102 and GS-US-236-0103 provides EVG and COBI exposures with maximal antiviral efficacy, FTC exposures bioequivalent to stand-alone capsule, and TFV exposures that are modestly higher relative to the TDF stand-alone tablet (~26% AUC_{tau}; based on COBI inhibition of intestinal Pgp), but comparable with those from TDF-containing regimens used clinically, including RPV and RTV-boosted PIs (eg, ~24% with RPV, ~37% with ATV/r, ~22% with DRV/r, ~32% with LPV/r) {8510}, {11255}.

5.1.2. Food Effect

Study GS-US-236-0105 evaluated the effect of food (under fasted conditions and 2 different fed conditions: light and high-fat meal) on the PK of EVG, COBI, FTC, and TFV. COBI exposure parameters AUC_{inf}, AUC_{0-last}, and C_{max} were bioequivalent under the light meal and fasted conditions; minor decreases (ranging from 19% to 27%) observed with a high-calorie/high-fat meal relative to the fasted state did not affect COBI's ability to appropriately boost EVG exposure. As expected due to EVG's low aqueous solubility, maximum increases in exposure (AUC_{inf}: 87% and C_{max}: 56%) were seen following a high-calorie/high-fat meal versus the fasted state. Modest increases were noted in EVG exposure (AUC_{inf}: 34%, and C_{max}: 22%) when administered with a light meal versus the fasted state. Fed conditions/light meal provide representative reference exposures, given the administration of the QUAD STR with food without specific requirements of meal type in Phase 2/3 studies. The differences in EVG exposure between light and high-fat meal are not considered to be clinically relevant, based on PK/PD results demonstrating comparable efficacy and safety profile across various EVG exposure quantiles.

FTC and TFV exposures were consistent with their established food effect profiles; FTC exposures were unaffected regardless of meal type versus the fasted state and TFV exposures resulting from the QUAD tablet were modestly higher with food relative to administration of TDF in the fasted state (light meal: AUC_{inf}: 24% and C_{max}: 20%; high-fat meal: AUC_{inf}: 23% and no change in C_{max}).

Given the higher EVG exposures achieved under fed conditions and the desire to provide maximal antiviral activity, including in the setting of late or missed doses, the QUAD STR was administered with food in its clinical development program. The proposed product labeling recommends the QUAD STR be taken with food to achieve a high mean IQ (IQ_{95}: ~10). EVG C_{24hr} following QUAD STR administration under fasted conditions provides an IQ_{95} ~5; based on the robust trough concentrations and low PK variability, as such, efficacious EVG exposures are still expected in the setting of QUAD administration in the setting of a fasted administration.

5.1.3. Clinical Pharmacodynamics

In addition to systematic PK/PD evaluation in dose-finding studies, safety PK/PD studies were conducted to evaluate the proarrhythmic potential (QTc prolongation) of EVG and COBI in accordance with ICH E13 guidance (Studies GS-US-183-0128 and GS-US-216-0107, respectively), the effect of COBI on LV function assessed by ECHOs

(Study GS-US-216-0116), and the effect of COBI on renal function, ie, estimated vs actual GFR in subjects with normal and also with mild/moderate renal impairment (Study GS-US-216-0121).

5.1.3.1. EVG

5.1.3.1.1. Efficacy PK/PD

In Study GS-US-183-0101, EVG was administered as monotherapy to antiretroviral treatment-naive or treatment-experienced HIV-1 infected subjects for 10 consecutive days at doses of 200, 400, or 800 mg twice daily; 800 mg once daily; or EVG 50 mg + RTV 100 mg once daily. EVG significantly reduced HIV-1 RNA levels compared with placebo at all dose levels; the 800 mg once daily, 200 mg twice daily, 400 mg twice daily, 800 mg twice daily, and 50 mg + RTV 100 mg once-daily doses resulted in maximum mean declines from baseline of 0.98, 1.48, 1.94, 1.91, and 1.99 $\log_{10}$ copies/mL, respectively. PK/PD analyses indicated that antiviral activity was best associated with EVG trough concentrations (rather than C_{max} or AUC), with an exposure/response relationship that was well described by a simple E_{max} model (E_{max} of 2.3 $\log_{10}$ reduction in HIV-1 RNA). The IQ (C_{trough}/IC_{95}: IQ_{95}) values for EVG were ~1 for 400 and 800 mg twice daily, and ~3 for 50 mg + RTV once daily.

Based on these PK/PD results, EVG was developed as a once-daily "boosted drug" to identify a dose that would be associated with a robust antiviral response and amenable to coformulation. In the Phase 2 study (GS-US-183-0105) in treatment-experienced HIV-1 infected subjects using EVG/r doses of 20, 50, and 125 mg, all 3 dose levels provided potent reduction in viral load at Week 2, and the EVG/r 125/100-mg group was statistically superior to the comparative PI in the analysis of difference between time-weighted average postbaseline and baseline $(DAVG)_{16}$, $DAVG_{24}$, and in categorical reductions in viral load. Accordingly, EVG exposures associated with 125/100-mg dose were selected for future development. Selection of this dose included consideration of the range of potential exposure of EVG in the broad HIV-1 infected patient population and that would be less impacted by late, missed or suboptimally administered doses. The final EVG dose of 150 mg was based on bioequivalent EVG exposures, including C_{trough} from the Phase 3 EVG formulation (used in Study GS-US-183-0145) compared with the 125-mg Phase 2 tablet {18914}.

For the QUAD STR, PK/PD analyses were performed in treatment-naive HIV-1 infected subjects in Phase 2 and 3 studies using EVG 150-mg exposures derived from population PK modeling. The relationship between EVG C_{trough} and antiviral activity (Week 2) was evaluated using the previously established E_{max} model from the proof of concept and EVG stand-alone Phase 2 study; EVG C_{trough} versus efficacy was assessed using virologic response (HIV-1 RNA < 50 copies/mL) at Week 48 in the Phase 3 study.

EVG 150 mg provided C_{trough} values that corresponded to the plateau phase of the exposure-antiviral activity relationship based on the E_{max} model. The results of EVG PK/PD analyses from the QUAD Phase 3 program using EVG C_{trough} and the corresponding virologic response using 3 different quantiles of PK exposure (quartiles, quintiles, or octiles) are

presented in Table 7. Virologic response was uniformly high across the categories of EVG C_{trough} by all approaches with no trends in exposure-response relationship. These results validate the selection of the 150-mg dose that provides exposures corresponding to maximal antiviral activity with both mean and all individual subject C_{trough} values that exceed the protein binding-adjusted IC_{95}.

Table 7. GS-US-236-0102 and GS-US-236-0103: Percentage of Virologic Responders Across Quantiles of EVG Exposure (N = 373) (EVG PK/PD Analysis Set)

EVG C_{trough} Quartile (ng/mL)	VR for HIV-1 RNA Cutoff of 50 copies/mL Within Each Quartile (%)	EVG C_{trough} Quintile (ng/mL)	VR for HIV-1 RNA Cutoff of 50 copies/mL Within Each Quintile (%)	EVG C_{trough} Octile (ng/mL)	VR for HIV-1 RNA Cutoff of 50 copies/mL Within Each Octile (%)
n = 93 to 94		**n = 74 to 75**		**n = 46 to 47**	
58 to < 296	89	58 to < 264	89	58 to < 208	87
296 to < 423	88	264 to < 383	89	208 to < 296	92
423 to < 560	93	383 to < 456	87	296 to < 359	94
560 to 2341	87	456 to < 610	95	359 to < 423	83
		610 to 2341	87	423 to < 475	89
				475 to < 561	96
				561 to < 703	85
				703 to 2341	89

C_{trough}, plasma concentration at the end of the dosing interval; EVG, elvitegravir; PK/PD, pharmacokinetic/pharmacodynamic

5.1.3.1.2. Safety PK/PD

Study GS-US-183-0128, evaluating therapeutic (125 mg) and supratherapeutic (250 mg, 2-fold higher) doses/exposures (in addition to placebo and active [moxifloxacin] controlled) of boosted EVG, demonstrated no effect of boosted EVG on QT interval, meeting the ICH E13 definition of a negative "thorough QT/QTc study" as the upper bound of the 90% confidence interval for the maximal observed change in QTc did not exceed 10 msec. No significant ECG or wave morphology changes associated with either boosted-EVG dose level (125 vs 250 mg boosted with 100 mg RTV) and no relationships between EVG concentrations and QTc intervals were observed. Additionally, no SAE, study discontinuations due to a treatment-emergent AE, clinical laboratory abnormality, or changes in vital signs or physical examination findings were observed.

For the QUAD STR, PK/PD analyses of the EVG exposure-safety relationship in Phase 2 and 3 studies in treatment-naive HIV-1 infected subjects indicated that EVG exposures were comparable regardless of the incidence of common AEs such as headache, nausea, or diarrhea, and no relevant exposure-AE trends were observed. The maximum increase from baseline in serum creatinine (or maximum decrease in $eGFR_{CG}$) was comparable across quartiles of EVG exposure and no relevant trends in exposure changes in laboratory parameters were noted.

5.1.3.2. COBI

5.1.3.2.1. Efficacy PK/PD

A dose-ranging study of RTV (20–200 mg) demonstrated that substantial inhibition of CYP3A (using probe substrate MDZ) is achieved at very low doses of mechanism-based inhibitors and yields desired improvements in oral bioavailability of EVG via reduction of first-pass metabolism. It also showed that RTV 100 mg provided maintenance of near-maximal inhibition of systemic clearance over the dosing interval and allows achievement of desired high EVG trough concentrations. At doses of RTV greater than 100 mg, no additional boosting of EVG was observed. These results were used in the study design of Study GS-US-216-0101, a single- and multiple-dose ranging study evaluating the safety, tolerability, PK, and PD of COBI.

In Study GS-US-216-0101, COBI was administered at a range of doses (50–200 mg) and exhibited nonlinear PK with respect to dose and time for first-pass effect, oral bioavailability, and reduced systemic clearance, consistent with a mechanism-based inhibitor. COBI apparent clearance was reduced 98% over the single-dose range and 95% over the multiple-dose range, reaching a nadir after single- or multiple-dose administration at $\geq$ 200 mg. Steady-state COBI levels were achieved after ~7 days.

In Study GS-US-216-0101, using the validated CYP3A probe MDZ to directly measure anti-CYP3A activity of both COBI and RTV 100 mg (active control), COBI effectively inhibited CYP3A metabolism at low dose (50 mg) and provided 93% to 95% inhibition of MDZ apparent clearance at 100 to 200 mg, comparable with RTV (95% inhibition), and boosting of MDZ systemic exposures throughout the 24-hour dosing interval following once-daily dosing.

Based on these results the ability of COBI 100 and 150 mg to boost EVG 150 mg as QUAD was evaluated in Study GS-US-236-0101. A QUAD tablet containing COBI 100 mg provided bioequivalent exposures as assessed by AUC_{tau} and C_{max}, but a 37% lower C_{trough} estimate relative to EVG/r 150/100 mg. In the QUAD STR containing COBI 150 mg, EVG C_{max} was bioequivalent and AUC_{tau} was comparable (upper bound of the 90% CI exceeded the bioequivalence criteria by 1%). Importantly, at this COBI dose (150 mg), adequate EVG trough concentrations (C_{trough}) were achieved (~10% higher vs EVG/r), with high IQ_{95} values (~10).

With administration as the QUAD STR in HIV-1 infected subjects, EVG exposures were associated with high rates of virologic response and corresponded to the plateau phase of its exposure-antiviral efficacy relationship, indicating adequate boosting of EVG by COBI.

5.1.3.2.2. Safety PK/PD

Study GS-US-216-0107, the thorough QT/QTc study conducted with COBI doses/exposures (AUC_{tau}) ~2- or 4-fold above therapeutic exposures (in addition to placebo and active [moxifloxacin] controlled), demonstrated a lack of significant ECG changes and met the ICH

E13 definition of a negative "thorough QT/QTc study" as the upper bound of the 90% confidence interval for the maximal observed change in QTc did not exceed 10 msec. No clinically significant AEs, ECG abnormalities, or changes in physical exams or vital signs were observed.

In Study GS-US-216-0107, an equivalent COBI exposure to 150 mg once daily was achieved with 250 mg at 2 hours after dosing (mean [%CV] concentration = 1269.4 [43] ng/mL). At this COBI exposure, the corresponding PR interval prolongation was 4.2 msec. This modest dose-related increase in PR interval was reversible over the dosing interval and was not considered to be clinically significant. The safety profile of EVG and COBI within the QUAD STR are further supported by data from Phase 2 and 3 studies (GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103), where none of 749 subjects who received the QUAD STR developed clinically significant first-, second-, or third-degree heart block (assessed by ECG). Nonclinically significant first-degree heart block was observed on ECG in 6 of 749 subjects (0.8%) in the QUAD group, 5 of 375 subjects (1.3%) in the Atripla group, and 8 of 355 subjects (2.3%) in the ATV/r+TVD group. No subjects reported any degree of heart block as AEs.

Study GS-US-216-0116 evaluated the effect of COBI at steady state on LV function using ECHOs and ECGs. In a nonclinical Langendorff study using isolated rabbit hearts, COBI prolonged the PR interval (first-degree atrioventricular block) and produced decreases in LV function and heart rate at concentrations $\geq$ 1.5 μM. These changes were at COBI concentrations approximately 11-fold higher than the unbound steady-state C_{max} with COBI 150 mg. Study GS-US-216-0116 demonstrated that COBI administration did not result in clinically relevant changes in the LV function in healthy human subjects.

During Phase 1 and 2 development, administration of COBI to healthy subjects and HIV-1 infected subjects was found to result in a small increase in serum creatinine. This was unexpected and led to detailed evaluation of the potential effect of COBI on estimated and actual GFR. Study GS-US-216-0121 evaluated the effect of COBI on renal function as assessed by markers of GFR in HIV-1 negative subjects with normal or mild/moderate renal impairment. This study was conducted after small, but consistent, changes in serum creatinine and eGFR were observed in Phase 1 and 2 studies. In this study, following 7 days of dosing with COBI, mean (SD) eGFR values decreased by 9.9 (13.14) mL/min and 11.9 (6.97) mL/min relative to baseline eGFR $\geq$ 80 mL/min and 50 to 79 mL/min, respectively. These changes were reversible and returned to baseline values following a 7-day washout period. The time to onset, magnitude, and time to resolution of the observed changes in eGFR are consistent with the inhibition of tubular secretion of creatinine by COBI. In contrast, GFR assessed via iohexol clearance (an exogenous GFR probe) was unchanged by COBI. These data indicated that COBI does not affect true renal glomerular function (aGFR) but affects eGFR, which is calculated using serum creatinine.

In pooled Phase 2 and 3 analyses, the maximum increase from baseline in serum creatinine (or maximum decrease in $eGFR_{CG}$) was comparable across COBI exposure quartiles and no relevant trends in exposure changes in laboratory parameters were noted.

PK/PD analyses of the COBI exposure-safety relationship that were performed in Phase 2 and 3 studies in treatment-naive HIV-1 infected subjects indicated that COBI exposures were comparable regardless of the incidence of common AEs such as headache, nausea, or diarrhea, and no relevant exposure-AE trends were observed.

5.1.4. Clinical Pharmacokinetics

5.1.4.1. Pharmacokinetic Profile

As demonstrated in the clinical pharmacology studies, EVG coadministered with either RTV 100 mg or COBI 150 mg has a PK profile appropriate for once-daily dosing. Boosted EVG exhibits less than dose-proportional increases in exposure over the dose range of 20 to 300 mg, likely due to decreased absorption related to solubility-limited dissolution. EVG displays higher bioavailability upon administration with food. Because EVG is metabolized via CYP3A, administration of EVG with a boosting agent substantially increases the relative oral bioavailability of EVG and reduces its apparent clearance, resulting in longer plasma half-life (~9 hours boosted vs ~3 hours unboosted) and trough concentrations (C_{trough}) appropriate for once-daily dosing. A clinical study that evaluated EVG PK with a range of coadministered RTV doses demonstrated that 100 mg RTV once daily provides maximal boosting of EVG exposure; COBI at 150 mg provides equivalent CYP3A inhibition and EVG exposure compared with RTV 100 mg.

5.1.4.2. Absorption, Distribution, Metabolism, and Excretion (ADME)

5.1.4.2.1. EVG

Following oral administration of EVG, peak concentrations are observed ~3 to 4 hours after dosing and its absorption is unaffected by local GI pH. As with other HIV integrase inhibitors, EVG is subject to chelation by high concentrations of di- and tri-valent cations, such as with high-strength antacids in the GI tract; therefore administration with acid-lowering agents should be staggered by at least 2 hours. The oral bioavailability of boosted EVG is high based on comparisons of exposure following unboosted versus boosted administration.

Based on equilibrium dialysis studies, EVG was on average 98% to 99% bound to human plasma proteins regardless of concentration, with preferential binding to albumin over α_1-acid glycoprotein. The distribution of EVG into peripheral compartments (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated, but penetration of EVG to the brain in nonclinical species was very low and unaffected by RTV pretreatment.

EVG undergoes hepatic metabolism and is minimally excreted in the urine. Primary metabolites of EVG are M1, produced by CYP3A4 and inhibited by COBI, and M4, produced by UGT1A1/3. The M1 and M4 metabolites are markedly less potent (M1: 5- to 18-fold and M4: 10- to 38-fold in antiviral activity assays) than parent drug; therefore the metabolites are not considered to contribute to the antiviral activity of EVG.

EVG is not a clinically relevant inhibitor of CYP enzymes or Pgp and is a weak/modest activator of PXR.

5.1.4.2.2. COBI

The pharmacokinetics of COBI have been evaluated over a dose range of 50 to 400 mg. Plasma concentrations of COBI increased in a greater-than-proportional manner relative to the increase in dose, and this effect was greater with multiple-dose administration than with single-dose administration. The half-life of COBI upon multiple dosing is ~3 hours; however, its pharmacodynamic effect on inhibiting CYP3A and boosting EVG exposures persists over the 24-hour dosing interval. These data are expected and are consistent with its mechanism of action as a mechanism-based inhibitor of CYP3A.

Following oral administration, peak COBI concentrations are observed ~4 to 5 hours after dosing, and its absorption is not influenced by GI pH. In clinical studies, COBI was administered in the QUAD STR with food, based on the dosing recommendation for EVG.

Based on equilibrium dialysis studies, COBI was on average 97% to 98% bound to human plasma proteins independent of concentration. The distribution of COBI into peripheral compartments (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

COBI undergoes hepatic metabolism; excretion in the urine, mainly as unchanged drug, is minor. COBI is extensively metabolized in vitro via CYP3A (major) and CYP2D6 (minor) mediated oxidation and there is no evidence of direct Phase 2 metabolism.

Mean circulating plasma exposure of COBI metabolites was < 3% of COBI exposure (AUC) at the 150-mg dose in clinical studies.

5.1.4.2.3. TFV and FTC

The plasma PK of FTC and TFV were evaluated for the QUAD STR using the FTC 200-mg capsule and the TDF 300-mg tablet as reference. Exposures of FTC were bioequivalent following administration of the QUAD STR versus FTC capsule. TFV AUC_{tau} was 26% higher in the QUAD STR versus reference, consistent with the inhibition of intestinal Pgp-mediated secretory (efflux) transport of TDF by COBI (due to high intestinal concentrations). The transient inhibition of Pgp by COBI is similar to the inhibitory effect of RTV, which results in a modest increase in TFV exposures upon TDF coadministration with several antiretrovirals, including boosted PIs; TDF exposures (AUC_{tau}) in Phase 1 studies were higher relative to TDF dosing alone (37%, 22%, 32%, and 24% with ATV/r, DRV/r, LPV/r, and RPV, respectively). The safety profile of TFV in studies achieving these exposures has been well characterized {15873}, {14062}, {12302}, {14592}, {14110}, {14108}, {18498}, {9341}, {12249}, {19273}, {18038}, {19105}, {10921}, {7013}, {10961}, {13023}, {19102}, {11299}. No additive or synergistic effects of TFV and COBI are expected in the kidney.

5.1.4.3. Renal or Moderate Hepatic Impairment

No clinically relevant changes in EVG or COBI exposures are observed in the setting of severe renal or moderate hepatic impairment. Dose adjustment of these agents is not warranted in these populations. However, dose-interval adjustments required for FTC and TDF in patients with $eGFR_{CG}$ < 50 mL/min cannot be achieved with the fixed-dose combination QUAD tablet; therefore, QUAD should be discontinued in patients for whom $eGFR_{CG}$ declines to < 50 mL/min. No data are available regarding the use of EVG or COBI in subjects with severe hepatic impairment; therefore the QUAD STR is not recommended for use in patients with severe hepatic impairment.

5.1.4.4. Demographic Variables

In a population PK analysis of EVG from 9 studies, including 161 healthy subjects and 419 HIV-1 infected subjects, no relevant effects of age, sex (male, female), race (Asian, black, white), baseline eGFR, hepatitis B or C coinfection, HIV status (positive or negative), or COBI 150-mg exposures were observed on EVG exposures. A modest, but statistically significant inverse relationship was observed between EVG exposures and body surface area (BSA) that was not considered clinically relevant (15% difference in EVG trough concentrations between the lowest and highest quartiles of BSA).

Consistent with established profiles for FTC or TFV, no clinically significant differences in the absorption, distribution, metabolism, and excretion (ADME) profiles for FTC or TFV are expected due to demographic factors with the QUAD STR.

5.1.4.5. Drug-Drug Interaction Profile

The QUAD STR is intended for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral drugs.

The drug-drug interaction profile for QUAD is characterized by the combined profiles of its components. The N(t)RTI backbone of FTC/TDF has a well-established drug-drug interaction profile and no dose adjustments are required on coadministration with concomitant medications. Based on in vitro and clinical studies, COBI administration would result in potent inhibition of CYP3A. Due to this effect, similar to RTV-boosted PIs, narrow therapeutic index agents that are substrates for CYP3A are contraindicated for use with QUAD or have monitoring and/or dosing recommendations upon coadministration; well known CYP3A inducers may result in lower exposures of EVG and/or. Table 8 presents concomitant agents that are contraindicated with QUAD based on these considerations, which are typically also contraindicated with RTV-boosted PIs. COBI administration results in weak inhibition of CYP2D6 (25% and 65% increase in C_{max} and $AUC_{inf,}$ respectively, of probe 2D6 substrate desipramine), and transient intestinal inhibition of Pgp (41% increase in Cmax and no change in AUC of probe substrate digoxin).

Table 8. Agents Contraindicated due to the Potential for Serious and/or Life-Threatening Events or Loss of Virologic Response and Possible Resistance to QUAD

Class	Agent
Alpha 1-adrenoreceptor antagonist	alfuzosin
Antimycobacterial	rifampin, rifabutin
Ergot derivatives	dihydroergotamine, ergometrine, ergotamine
GI motility agent	cisapride
Herbal products	St. John's wort (*Hypericum perforatum*)
HMG CoA reductase inhibitors	lovastatin, simvastatin
Neuroleptic	pimozide
PDE-5 inhibitors	Sildenafil and tadalafil for treatment of pulmonary arterial hypertension
Sedative/hypnotics	orally administered midazolam, triazolam

HMG CoA, 3-hydroxy-3-methyl-glutaryl-CoA

EVG is a modest PXR activator that can induce CYP3A (induction effect blocked by COBI), and other isozymes such as CYP2C enzymes, also noted with the low, boosting dose of RTV and with a RTV-boosted PI. As such, clinical management of concomitant medications with the QUAD STR is expected to be comparable with that of RTV-boosted PIs.

Coadministration with antacids should be staggered from QUAD STR dosing by at least 2 hours due to a chelating effect of antacids (due to high concentrations of divalent cations) with EVG (consistent with other integrase inhibitors). EVG and COBI exposures are not affected by coadministration with acid-lowering agents.

Due to the desire to provide and maintain high EVG trough concentrations associated with high antiviral activity QUAD should not be coadministered with CYP3A inducers, as these could decrease COBI and subsequently EVG plasma concentrations, and potentially reduce the therapeutic effect of EVG.

Due to slightly reduced exposures of ethinyl estradiol (EE) upon coadministration, it is recommended that such contraceptive medications contain at least 30 µg of EE when coadministered with the QUAD STR. A recommendation for dose adjustment of EE has also been proposed with ATV/r. The dose adjustment of EE with the QUAD STR is more permissive than that for other RTV-boosted PIs, in particular DRV/r for which coadministration of contraceptive medications is not recommended.

Appropriate guidance regarding potentially clinically significant drug interactions in the HIV-1 infected population was based on clinical experience with use of concomitant medications during treatment with the individual agents (EVG and COBI) as well as the QUAD STR, including preclinical and clinical drug-drug interaction evaluations.

6. OVERVIEW OF PHASE 2 AND 3 CLINICAL DEVELOPMENT PROGRAM

6.1. Principal QUAD STR Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

The principal safety and efficacy studies for the QUAD STR are Phase 2 Study GS-US-236-0104 and Phase 3 Studies GS-US-236-0102 and GS-US-236-0103. Safety and efficacy data from the QUAD NDA data cut are presented in this document. Selected safety data from the QUAD NDA safety update are also presented. Statistical methods for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 are presented in Appendix 3.

The main study designs and population characteristics are summarized in Table 9. Study populations were antiretroviral treatment-naive, HIV-1 infected subjects with HIV-1 RNA ≥ 5000 copies/mL at screening, with no prior use of any approved or experimental antiretroviral drug. In all 3 studies, randomization was stratified by HIV-1 RNA at screening (≤ 100,000 copies/mL or > 100,000 copies/mL). In these 3 studies, the comparator arm contained the US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada) and a preferred third agent (ie, the NNRTI EFV [given as the Atripla STR] in GS-US-236-0104 and GS-US-236-0102 and ATV/r in GS-US-236-0103).

In Study GS-US-236-0104, subjects were enrolled in a total of 30 study sites in the US. In Study GS-US-236-0102, subjects were enrolled in a total of 102 study sites; 97 in the US and 5 in Puerto Rico. In Study GS-US-236-0103, subjects were enrolled in a total of 146 study sites; 88 in the US and 58 in other countries.

In Study GS-US-236-0104, screening genotype reports had to show no NRTI, NNRTI, or primary PI resistance mutations (by current International Antiviral Society–United States of America [IAS-USA] guidelines {13428}). In the Phase 3 studies, screening genotype reports had to show sensitivity to the drugs in the comparator arm (EFV, FTC, and TDF [GS-US-236-0102] or ATV [GS-US-236-0103]).

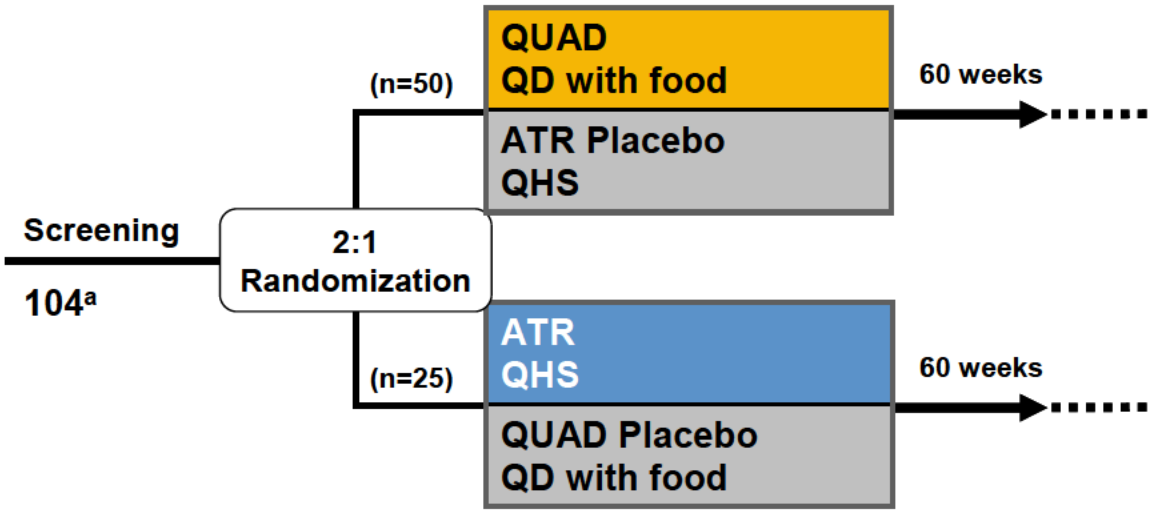
Because the Phase 3 studies were double blind and double dummy to support registration of the product, the evaluation of the benefit of STRs on drug adherence is confounded by the need for subjects to take additional pills required for blinding.

Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 are outlined below.

6.1.1.1. Study GS-US-236-0104

Study GS-US-236-0104 is a Phase 2, double-dummy, randomized, double-blind, multicenter, multiple-dose, active-controlled study evaluating the safety and efficacy of the QUAD STR versus Atripla in 71 HIV-1 infected, antiretroviral treatment-naive adult subjects (Figure 3). The 48-week, double-blind randomization period of Study GS-US-236-0104 has been completed. Subjects were randomized in a 2:1 ratio to either QUAD + Atripla placebo or Atripla + QUAD placebo. Subjects were treated with double-blind study drug for 48 weeks. The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24. The primary analysis for the primary efficacy endpoint was the missing = failure (M=F) method. The study has been unblinded, and the primary endpoint has been analyzed (Section 7.1.1.1). At the Week 60 visit, subjects were offered the option to participate in an ongoing open-label, single-arm study extension for treatment with the QUAD STR.

Figure 3. GS-US-236-0104: Study Design



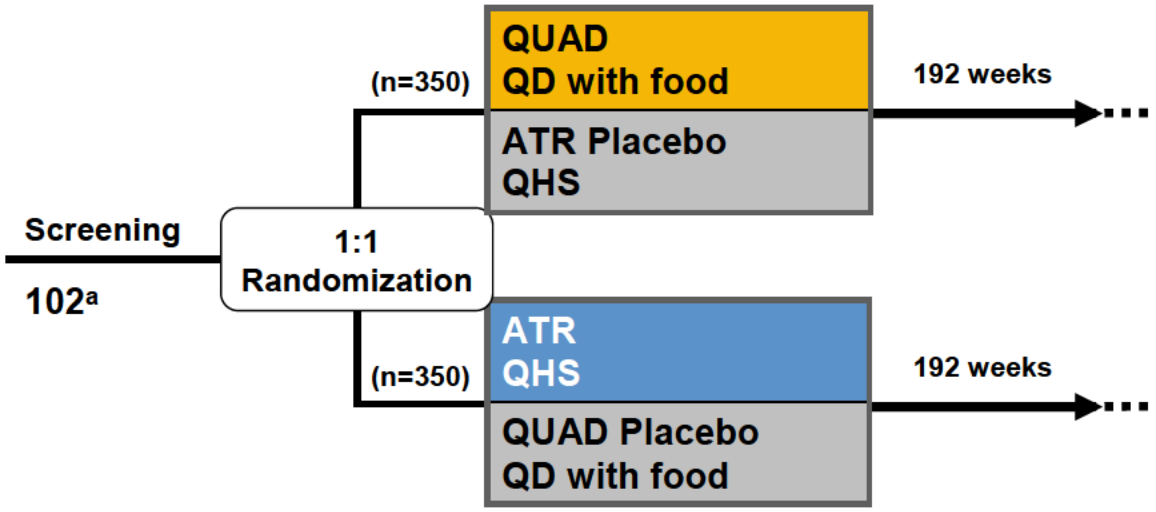
ATR, Atripla; QD, once daily; QHS, once daily prior to bedtime

a Stratification by HIV-1 RNA > 100,000 copies/mL

6.1.1.2. Study GS-US-236-0102

Study GS-US-236-0102 is a Phase 3, double-dummy, randomized, double-blind, multicenter, multiple-dose, active-controlled study evaluating the safety and efficacy of the QUAD STR versus the Atripla STR in HIV-1 infected antiretroviral treatment-naive adult subjects (Figure 4). A total of 707 subjects were randomized in a 1:1 ratio to either QUAD + Atripla placebo or Atripla + QUAD placebo. During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 192. After Week 192, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover extension study in which all subjects will be treated with the QUAD STR. The primary efficacy endpoint was the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis (Appendix 3). The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the QUAD STR compared with the Atripla STR using a conventional 95% CI approach, with a noninferiority margin of 12%. The double-blind phase of the study is ongoing; however, the 48-week primary endpoint has been analyzed.

Figure 4. GS-US-236-0102: Study Design



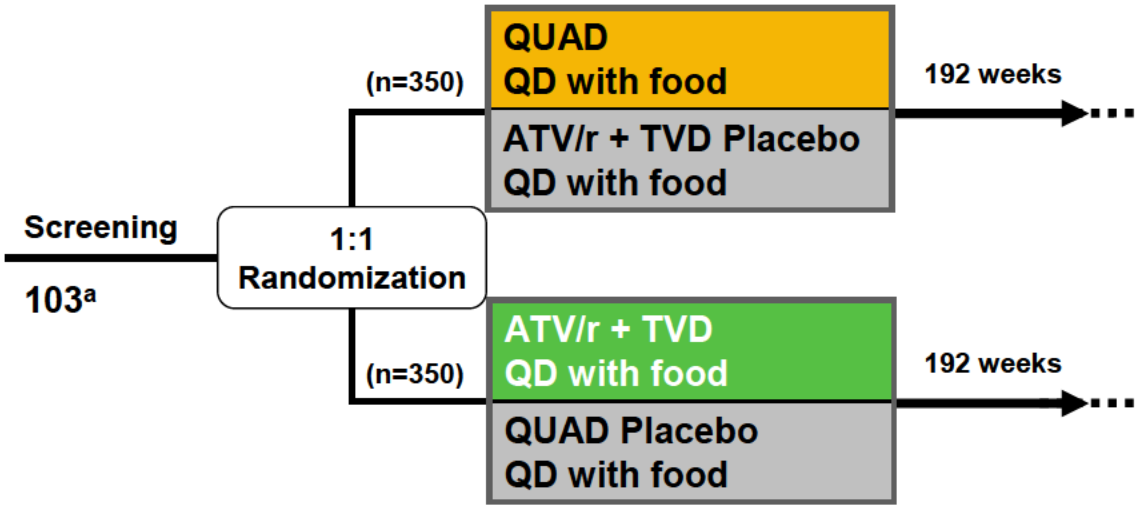
ATR, Atripla; QD, once daily; QHS, once daily prior to bedtime

a Stratification by HIV-1 RNA > 100,000 copies/mL

6.1.1.3. Study GS-US-236-0103

Study GS-US-236-0103 is a Phase 3, double-dummy, randomized, double-blind, multicenter, multiple-dose, active-controlled study evaluating the safety and efficacy of the QUAD STR versus ATV/r+TVD in HIV-1 infected, antiretroviral treatment-naive adult subjects (Figure 5). A total of 715 subjects were randomized in a 1:1 ratio to either QUAD + ATV/r+TVD placebo or ATV/r+TVD + QUAD placebo. During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover extension study in which all subjects will be treated with the QUAD STR. The primary efficacy endpoint was the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis (Appendix 3). The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the QUAD STR compared with ATV/r+TVD using a conventional 95% CI approach, with a noninferiority margin of 12%. The double-blind phase of the study is ongoing; however, the 48-week primary endpoint has been analyzed.

Figure 5. GS-US-236-0103: Study Design



ATV/r, ritonavir-boosted atazanavir; QD, once daily; TVD, Truvada

a Stratification by HIV-1 RNA > 100,000 copies/mL

Table 9. Tabular Summary of Key Clinical Studies Relevant to the QUAD STR for HIV-1 Infection

Study Number	Design	Primary and Secondary Efficacy Endpoints	Population	Treatment Groups	Treatment Duration and Status	Number of Subjects by Treatment
GS-US-236-0104	Phase 2, double-blind, double-dummy, multicenter, randomized, active-controlled study	The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24. The secondary efficacy endpoints were as follows: The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 Virologic outcomes at Weeks 24 and 48 using the FDA-defined snapshot analysis and HIV-1 RNA < 50 copies/mL The changes from baseline in HIV-1 RNA (log_{10} copies/mL) and CD4 cell count and percentage at Weeks 24 and 48	HIV-1 infected, antiretroviral treatment-naive adults with HIV-1 RNA ≥ 5000 copies/mL, CD4 cell count > 50 cells/μL, $eGFR_{CG}$ ≥ 80 mL/min at screening and with no NRTI, NNRTI, or primary PI resistance mutations	STR containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg (QUAD) once daily + placebo for ATR once daily prior to bedtime Or STR containing EFV 600 mg/ FTC 200 mg/ TDF 300 mg (ATR) once daily prior to bedtime + placebo for QUAD once daily	60 weeks of double-blind treatment, followed by optional open-label QUAD extension until study drug is commercially available or study terminated by sponsor	Randomized: 71 (48 QUAD and 23 ATR) Completed randomized phase: 65 (45 QUAD and 20 ATR) Entered open-label extension: 59 (45 QUAD and 14 ATR)

Study Number	Design	Primary and Secondary Efficacy Endpoints	Population	Treatment Groups	Treatment Duration and Status	Number of Subjects by Treatment
GS-US-236-0102	Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study	The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA-defined snapshot analysis. The secondary efficacy endpoint evaluated for the Week 48 analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL (based on the FDA-defined TLOVR algorithm).	HIV-1 infected, antiretroviral treatment-naive adults with HIV-1 RNA ≥ 5000 copies/mL and $eGFR_{CG} \geq 70$ mL/min at screening, with no prior use of any approved or experimental antiretroviral drug, and sensitivity to EFV, FTC, and TDF, as demonstrated by the subject's HIV-1 genotype at screening	STR containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg (QUAD) once daily + placebo for ATR once daily prior to bedtime Or STR containing EFV 600 mg/ FTC 200 mg/ TDF 300 mg (ATR) once daily prior to bedtime + placebo for QUAD once daily	192 weeks of double-blind treatment; after Week 192, subjects will continue to take their blinded study drug until treatment assignments have been unblinded, at which point all subjects will be given the option to participate in an open-label rollover study until study drug is commercially available or study terminated by sponsor	Randomized: 707 (353 QUAD and 354 ATR) Subjects still on study treatment up to the Week 48 analysis data cut date: 617 (311 QUAD and 306 ATR) Subjects still on study up to the Week 48 analysis data cut date: 635 (319 QUAD and 316 ATR)

Study Number	Design	Primary and Secondary Efficacy Endpoints	Population	Treatment Groups	Treatment Duration and Status	Number of Subjects by Treatment
GS-US-236-0103	Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study	The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA-defined snapshot analysis. The secondary efficacy endpoint evaluated for the Week 48 analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL (based on the FDA-defined TLOVR algorithm).	HIV-1 infected, antiretroviral treatment-naive adults with HIV-1 RNA ≥ 5000 copies/mL and $eGFR_{CG} \geq 70$ mL/min at screening, with no prior use of any approved or experimental antiretroviral drug, and sensitivity to ATV, FTC, and TDF, as demonstrated by the subject's HIV-1 genotype at screening	STR containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg (QUAD) once daily + placebos for RTV, ATV, and TVD once daily RTV 100 mg + ATV 300 mg + FTC 200 mg/ TDF 300 mg once daily at approximately the same time each day + placebo for QUAD once daily	192 weeks of double-blind treatment; after Week 192, subjects will continue to take their blinded study drug until treatment assignments have been unblinded, at which point all subjects will be given the option to participate in an open-label rollover study until study drug is commercially available or study terminated by sponsor	Randomized: 715 (357 QUAD and 358 ATV/r+TVD) Subjects still on study treatment up to the Week 48 analysis data cut date: 635 (320 QUAD and 315 ATV/r+TVD) Subjects still on study up to the Week 48 analysis data cut date: 655 (331 QUAD and 324 ATV/r+TVD)

ATR, Atripla; ATV, atazanavir; CD4, cluster of differentiation 4; COBI, cobicistat; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; EFV, efavirenz; EVG, elvitegravir; FDA, United States Food and Drug Administration; FTC, emtricitabine; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QUAD, EVG/COBI/FTC/TDF; RTV, ritonavir; STR, single-tablet regimen; TDF, tenofovir disoproxil fumarate; TLOVR, time to loss of virologic response; TVD, Truvada

6.1.1.4. Demographic and Baseline Characteristics in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

Demographics and baseline characteristics for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 are displayed in Table 10 and Table 11.

Overall, demographic and baseline characteristics in the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 were similar in each treatment group. The majority of subjects (89.8%) were male, with a mean age of 38 years (range, 18–72 years), and most were white (68.9%) or black (22.5%) and non-Hispanic/Latino (79.7%). Mean (SD) baseline values were as follows: HIV-1 RNA 4.77 (0.599) $\log_{10}$ copies/mL; CD4 cell count 379 (174.8) cells/µL; and CD4% 22.2 (8.31). Overall, 63.4% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL and 36.6% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. The majority of subjects (82.8%) had asymptomatic HIV-1 infection.

Table 10. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Demographics and Baseline Characteristics (Pooled Safety Analysis Set)

Characteristic[a]	QUAD 236-0102, 0103, 0104 (N = 749)	ATR 236-0102, 0104 (N = 375)	ATV/r+TVD 236-0103 (N = 355)	Total (N = 1479)
Age (Years)				
N	749	375	355	1479
Mean (SD)	37 (10.4)	38 (10.6)	39 (9.8)	38 (10.3)
Median	37	38	39	37
Q1, Q3	29, 45	29, 45	31, 46	30, 45
Min, Max	18, 72	18, 67	19, 69	18, 72
Sex				
Male	675 (90.1%)	337 (89.9%)	316 (89.0%)	1328 (89.8%)
Female	74 (9.9%)	38 (10.1%)	39 (11.0%)	151 (10.2%)
Race				
American Indian or Alaska Native	5 (0.7%)	4 (1.1%)	3 (0.8%)	12 (0.8%)
Asian	24 (3.2%)	10 (2.7%)	17 (4.8%)	51 (3.4%)
Black or African Heritage	190 (25.4%)	96 (25.6%)	47 (13.2%)	333 (22.5%)
Native Hawaiian or Pacific Islander	5 (0.7%)	1 (0.3%)	2 (0.6%)	8 (0.5%)
White	497 (66.4%)	245 (65.3%)	277 (78.0%)	1019 (68.9%)
Other	28 (3.7%)	19 (5.1%)	9 (2.5%)	56 (3.8%)
Ethnicity				
Hispanic/Latino	150 (20.0%)	88 (23.5%)	47 (13.2%)	285 (19.3%)
Non-Hispanic/ Latino	594 (79.3%)	287 (76.5%)	298 (83.9%)	1179 (79.7%)
Not Permitted[b]	5 (0.7%)	0	10 (2.8%)	15 (1.0%)
Baseline Weight (kg)				
N	749	375	355	1479
Mean (SD)	80.4 (17.75)	81.3 (16.81)	79.7 (16.04)	80.4 (17.11)
Median	77.6	78.0	77.5	77.8
Q1, Q3	68.9, 88.0	70.3, 90.9	68.0, 88.0	69.0, 88.4
Min, Max	42.0, 174.2	47.6, 163.7	47.0, 153.3	42.0, 174.2

Characteristic[a]	QUAD 236-0102, 0103, 0104 (N = 749)	ATR 236-0102, 0104 (N = 375)	ATV/r+TVD 236-0103 (N = 355)	Total (N = 1479)
Baseline Height (cm)				
N	749	375	355	1479
Mean (SD)	175.7 (8.87)	176.0 (8.95)	175.7 (8.55)	175.8 (8.81)
Median	177.0	177.8	176.0	177.0
Q1, Q3	170.2, 180.3	170.2, 182.9	170.2, 181.6	170.2, 181.6
Min, Max	132.0, 205.7	142.2, 198.1	149.0, 200.0	132.0, 205.7
Baseline Body Mass Index (kg/m^2)				
N	749	375	355	1479
Mean (SD)	26.0 (5.53)	26.2 (5.16)	25.8 (4.80)	26.0 (5.27)
Median	25.0	25.2	25.0	25.1
Q1, Q3	22.4, 28.0	22.9, 28.5	22.3, 28.1	22.5, 28.2
Min, Max	15.8, 53.2	16.5, 53.3	17.8, 51.4	15.8, 53.3

ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; Q1, first quartile; Q3, third quartile; TVD, Truvada

a The denominator for percentages is based on the number of subjects in the safety analysis set.

b Regulators do not allow collection of ethnicity information.

Table 11. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Baseline Disease Characteristics (Pooled Safety Analysis Set)

Characteristic[a]	QUAD 236-0102, 0103, 0104 (N = 749)	ATR 236-0102, 0104 (N = 375)	ATV/r+TVD 236-0103 (N = 355)	Total (N = 1479)
HIV-1 RNA (log_{10} copies/mL)				
N	749	375	355	1479
Mean (SD)	4.77 (0.605)	4.77 (0.565)	4.80 (0.619)	4.77 (0.599)
Median	4.78	4.77	4.86	4.79
Q1, Q3	4.32, 5.16	4.35, 5.14	4.38, 5.21	4.35, 5.16
Min, Max	1.69, 6.58	3.03, 6.54	2.98, 6.63	1.69, 6.63
HIV-1 RNA Categories (copies/mL)				
≤ 100,000	470 (62.8%)	254 (67.7%)	214 (60.3%)	938 (63.4%)
> 100,000	279 (37.2%)	121 (32.3%)	141 (39.7%)	541 (36.6%)
CD4 Cell Count (/μL)				
N	749	375	355	1479
Mean (SD)	377 (184.5)	386 (169.2)	375 (158.9)	379 (174.8)
Median	360	388	366	367
Q1, Q3	268, 472	273, 484	274, 466	271, 474
Min, Max	5, 1348	3, 1003	10, 963	3, 1348
CD4 Cell Count Categories (/μL)				
≤ 50	19 (2.5%)	6 (1.6%)	5 (1.4%)	30 (2.0%)
51 to ≤ 200	85 (11.3%)	45 (12.0%)	34 (9.6%)	164 (11.1%)
201 to ≤ 350	251 (33.5%)	104 (27.7%)	124 (34.9%)	479 (32.4%)
351 to ≤ 500	249 (33.2%)	141 (37.6%)	122 (34.4%)	512 (34.6%)
> 500	145 (19.4%)	79 (21.1%)	70 (19.7%)	294 (19.9%)
HIV Disease Status				
Asymptomatic	615 (82.1%)	317 (84.5%)	293 (82.5%)	1225 (82.8%)
Symptomatic HIV Infections	71 (9.5%)	33 (8.8%)	38 (10.7%)	142 (9.6%)
AIDS	63 (8.4%)	25 (6.7%)	24 (6.8%)	112 (7.6%)

Characteristic[a]	QUAD 236-0102, 0103, 0104 (N = 749)	ATR 236-0102, 0104 (N = 375)	ATV/r+TVD 236-0103 (N = 355)	Total (N = 1479)
HBV Surface Antigen Status				
Positive	10 (1.3%)	9 (2.4%)	7 (2.0%)	26 (1.8%)
Negative	738 (98.5%)	366 (97.6%)	346 (97.5%)	1450 (98.0%)
Indeterminate	0	0	1 (0.3%)	1 (<0.1%)
Not Done	1 (0.1%)	0	1 (0.3%)	2 (0.1%)
HCV Antibody Status				
Positive	35 (4.7%)	15 (4.0%)	10 (2.8%)	60 (4.1%)
Negative	714 (95.3%)	360 (96.0%)	344 (96.9%)	1418 (95.9%)
Indeterminate	0	0	0	0
Not Done	0	0	1 (0.3%)	1 (<0.1%)
$eGFR_{CG}$ (mL/min)				
N	749	375	355	1479
Mean (SD)	120.9 (32.78)	121.1 (33.57)	119.4 (31.26)	120.6 (32.61)
Median	114.2	114.4	114.7	114.4
Q1, Q3	99.2, 135.3	98.5, 135.6	98.9, 134.7	99.0, 135.3
Min, Max	51.9, 355.3	60.8, 302.4	66.5, 333.2	51.9, 355.3

AIDS, acquired immune deficiency syndrome; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; CD4, cluster of differentiation 4; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; Q1, first quartile; Q3, third quartile; TVD, Truvada

a The denominator for percentages is based on the number of subjects in the safety analysis set.

b A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.

7. EFFICACY

7.1. Efficacy in Principal QUAD STR Studies (GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103)

In addition to individual study efficacy data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, pooled efficacy data for the primary endpoint up to the Week 48 cutoff dates (Week 60 for Study GS-US-236-0104) are presented. Data was pooled to maximize the number of subjects in each subgroup. Pooling of the study data was performed due to the similarities in study design and patient populations. The statistical analysis plan (SAP) for the pooled data was finalized before the Phase 3 studies were unblinded.

7.1.1. Efficacy in Study GS-US-236-0104

Key treatment outcomes for Study GS-US-236-0104 are presented in Table 12 and are briefly discussed below.

7.1.1.1. Primary Efficacy Endpoint

Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 (M=F)

Results of the primary endpoint analysis at Week 24 demonstrated high rates of virologic response in both the QUAD and Atripla groups. For the primary efficacy endpoint analysis, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 (ITT, M=F) was 89.6% (43 of 48 subjects) in the QUAD group and 87.0% (20 of 23 subjects) in the Atripla group. The difference in the response rate between the 2 treatment groups was 2.8% (95% CI: −14.5% to 20.1%).

7.1.1.2. Secondary Efficacy Endpoints

Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48 (M=F)

Results of the primary endpoint analysis at Week 48 demonstrated high rates of virologic response in both the QUAD and Atripla groups. Efficacy was maintained through Week 48. The proportion of subjects with suppression of plasma HIV-1 RNA < 50 copies/mL at Week 48 (ITT, M=F) was 89.6% (43 of 48 subjects) in the QUAD group and 87.0% (20 of 23 subjects) in the Atripla group.

Virologic Outcomes at Weeks 24 and 48 using Snapshot Analysis with HIV-1 RNA Cutoff < 50 copies/mL

Using snapshot analysis, the percentage of subjects with virologic success at Week 24 was 89.6% (43 of 48 subjects) in the QUAD group and 87.0% (20 of 23 subjects) in the Atripla group. The difference in the percentage of subjects with was 2.7% (95% CI: −15.4% to 20.9%). At Week 48, 91.7% of subjects (44 of 48) in the QUAD group and 82.6% of subjects

(19 of 23) in the Atripla group had virologic success. The difference in the percentage of subjects with virologic success was 9.2% (95% CI: –9.9% to 28.3%).

Change from Baseline in CD4 Cell Count

Mean baseline CD4 cell count was higher in the Atripla group compared with the QUAD group. Treatment with the QUAD STR resulted in an increase in mean CD4 cell count of 161 cells/µL from baseline to Week 24, which was greater than the mean increase observed in the Atripla group (117 cells/µL). Mean change from baseline in CD4 cell count remained higher in the QUAD group than the Atripla group at Week 48 (240 and 166 cells/µL, respectively).

Table 12. GS-US-236-0104: Key Treatment Outcomes (ITT Analysis Set)

Treatment Outcomes	QUAD (N = 48)	ATR (N = 23)	QUAD vs ATR Difference in Percentages (95% CI)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis[a]	44 (91.7%)	19 (82.6%)	9.2% (–9.9% to 28.3%)[b]
Virologic Responder at Week 24 (HIV-1 < 50 copies/mL; M=F)[c]	43 (89.6%)	20 (87.0%)	2.8% (–14.5% to 20.1%)[b]
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M=F)[c]	43 (89.6%)	20 (87.0%)	2.8% (–15.1% to 20.8%)[b]
Mean (SD) Change from Baseline in CD4 Cell Count at Week 48 (cells/µL)	240 (172.8)	166 (158.5)	74 (–15 to 164)[d]

ANOVA, analysis of variance; ATR, Atripla; CI, confidence interval; ITT, intent-to-treat; LSM, least-squares mean; MH, Mantel-Haenszel; M=F, missing = failure; SD, standard deviation

a Week 48 window is between Day 309 and 378 (inclusive).

b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c For M=F: Denominator for percentage was the number of subjects in the ITT analysis set.

d The difference in LSMs and its 95% CI were computed using an ANOVA model, including baseline HIV-1 RNA category in the model.

7.1.2. Efficacy in Study GS-US-236-0102

Key treatment outcomes for Study GS-US-236-0102 are presented in Table 13 and are briefly discussed below.

7.1.2.1. Primary Efficacy Endpoint

Virologic Outcomes at Week 48 using Snapshot Analysis with HIV-1 RNA Cutoff < 50 copies/mL

The results from the primary efficacy analysis demonstrated that QUAD once daily was noninferior to Atripla once daily when administered for 48 weeks to HIV-1 infected, antiretroviral treatment-naive adults. Based on the FDA-defined snapshot analysis, 87.6% of subjects (305 of 348) in the QUAD group and 84.1% of subjects (296 of 352) in the Atripla group had virologic success (ITT analysis set). The difference in the percentage of subjects with virologic success was 3.6% (95% CI: –1.6% to 8.8%). Sensitivity analyses to evaluate effects of study drug discontinuations not related to virologic response and late discontinuations also demonstrated that the QUAD STR was noninferior to Atripla. Subgroup analyses (ie, age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count) revealed high and generally comparable rates of virologic success with those observed for the overall study population (Figure 8).

7.1.2.2. Secondary Efficacy Endpoint

Virologic Outcomes at Week 48 using TLOVR Analysis with HIV-1 RNA Cutoff < 50 copies/mL

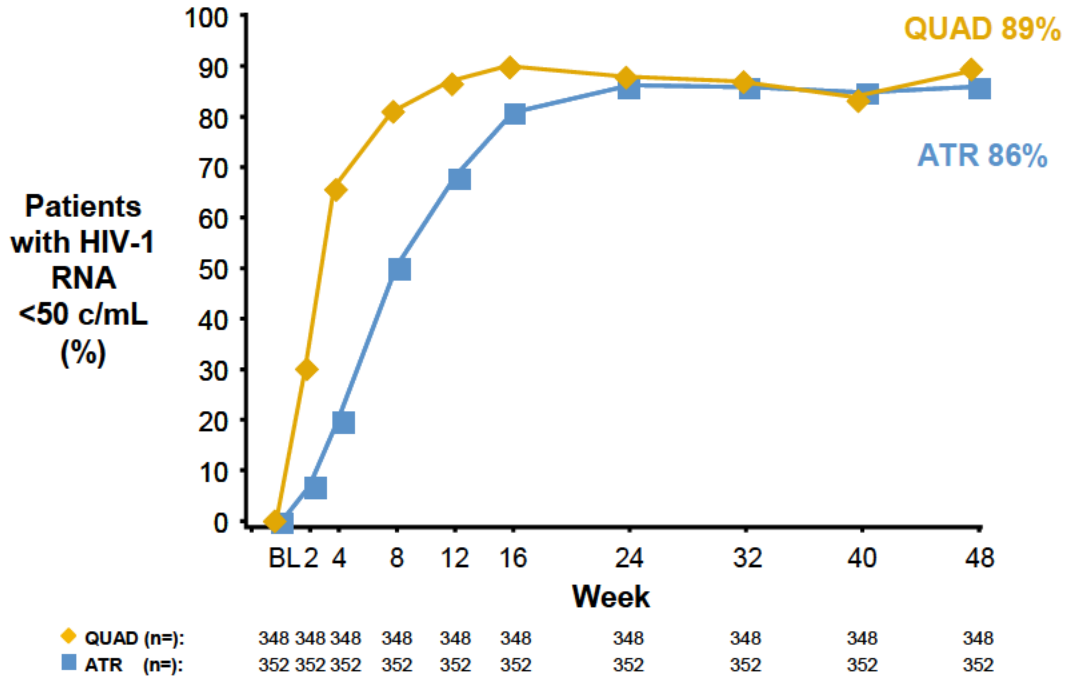
The FDA-defined TLOVR analysis results were consistent with the results of the snapshot analysis, confirming that the QUAD and Atripla STRs had comparable rates of virologic response. Based on the TLOVR analysis, 85.9% of subjects (299 of 348) in the QUAD group and 83.2% of subjects (293 of 352) in the Atripla group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The difference in the percentages of responders at Week 48 was 2.7% (95% CI: –2.6% to 8.1%), which is consistent with the results of the primary endpoint analysis.

7.1.2.3. Tertiary Efficacy Endpoints

Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using M=F and missing = excluded (M=E) methods were similar between treatments. In the M=F analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was significantly greater in the QUAD group than the Atripla group from Week 2 through Week 16; response rates between the 2 groups were similar from Week 24 through Week 48. At Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 88.8% (309 of 348) in the QUAD group and 85.5% (301 of 352) in the Atripla group (Figure 6). In the M=E analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 was 95.1% (309 of 325) in the QUAD group and 95.3% (301 of 316) in the Atripla group.

Figure 6. **GS-US-236-0102: Subjects with HIV-1 RNA < 50 Copies/mL (M=F)**



ATR, Atripla; BL, baseline; M=F, missing = failure

Change from Baseline in CD4 Cell Count

Mean (SD) baseline CD4 cell counts were 391 (188.6) cells/µL in the QUAD group and 382 (170.2) cells/µL in the Atripla group. CD4 cell counts increased following administration of study drug, and the mean increases were similar between the QUAD and Atripla groups, but were numerically higher in the QUAD group at all time points. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 239 (167.2) cells/µL in the QUAD group and 206 (153.4) cells/µL in the Atripla group. The difference in LSMs from an ANOVA model was 33 (95% CI: 8 to 58).

Table 13. GS-US-236-0102: Key Treatment Outcomes (ITT Analysis Set)

Treatment Outcomes	QUAD (N = 348)	ATR (N = 352)	QUAD vs ATR Difference in Percentages (95% CI)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis (n, %)[a]	305 (87.6%)	296 (84.1%)	3.6% (–1.6% to 8.8%)[b, c]
Virologic Responder (HIV-1 RNA < 50 copies/mL) at Week 48 using TLOVR Analysis (n, %)[a, d]	299 (85.9%)	293 (83.2%)	2.7% (–2.6% to 8.1%)[e]
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M=F) (n, %)[f]	309 (88.8%)	301 (85.5%)	3.3% (–1.6% to 8.3%)[e]
Mean (SD) Change from Baseline in CD4 cell count at Week 48 (cells/µL)	239 (167.2)	206 (153.4)	33 (8, 58)[g]

ATR, Atripla; CD4, cluster of differentiation 4; CI, confidence interval; IDMC, independent data monitoring committee; ITT, intent-to-treat; LSM, least-squares mean; M=F, missing = failure; MH, Mantel-Haenszel; TLOVR, time to loss of virologic response

a Week 48 window is between Day 309 and 378 (inclusive).

b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c At each of the 2 IDMC meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

d Responder refers to subjects who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.

e Difference in response rate (responder) and its 95% CI were from baseline HIV-1 RNA stratum-adjusted MH proportion.

f For the M=F analysis, denominator for percentage was the number of subjects in the ITT analysis set.

g The difference in LSMs and its 95% CI were computed adjusted for baseline HIV-1 RNA level.

7.1.3. Efficacy in Study GS-US-236-0103

Key treatment outcomes for Study GS-US-236-0103 are presented in Table 14 and are briefly discussed below. The results for GS-US-236-0103 were similar to those from GS-US-236-0102.

7.1.3.1. Primary Efficacy Endpoint

Virologic Outcomes at Week 48 using Snapshot Analysis with HIV-1 RNA Cutoff < 50 copies/mL

The results from the primary efficacy analysis demonstrated that QUAD once daily was noninferior to ATV/r+TVD once daily when administered for 48 weeks to HIV-1 infected, antiretroviral treatment-naive adults. Based on the FDA-defined snapshot analysis,

89.5% of subjects (316 of 353) in the QUAD group and 86.8% of subjects (308 of 355) in the ATV/r+TVD group had virologic success (ITT analysis set). The difference in the percentage of subjects with virologic success was 3.0% (95% CI: –1.9% to 7.8%). Sensitivity analyses to evaluate effects of study drug discontinuations not related to virologic response and late discontinuations also demonstrated that the QUAD STR was noninferior to ATV/r+TVD. Subgroup analyses (ie, age, sex, race, baseline HIV-1 RNA level, and baseline CD4 cell count) based on the FDA-defined snapshot analysis revealed high and generally comparable rates of virologic success with those observed for the overall study population (Figure 8).

7.1.3.2. Secondary Efficacy Endpoint

Virologic Outcomes at Week 48 using TLOVR Analysis with HIV-1 RNA Cutoff < 50 copies/mL

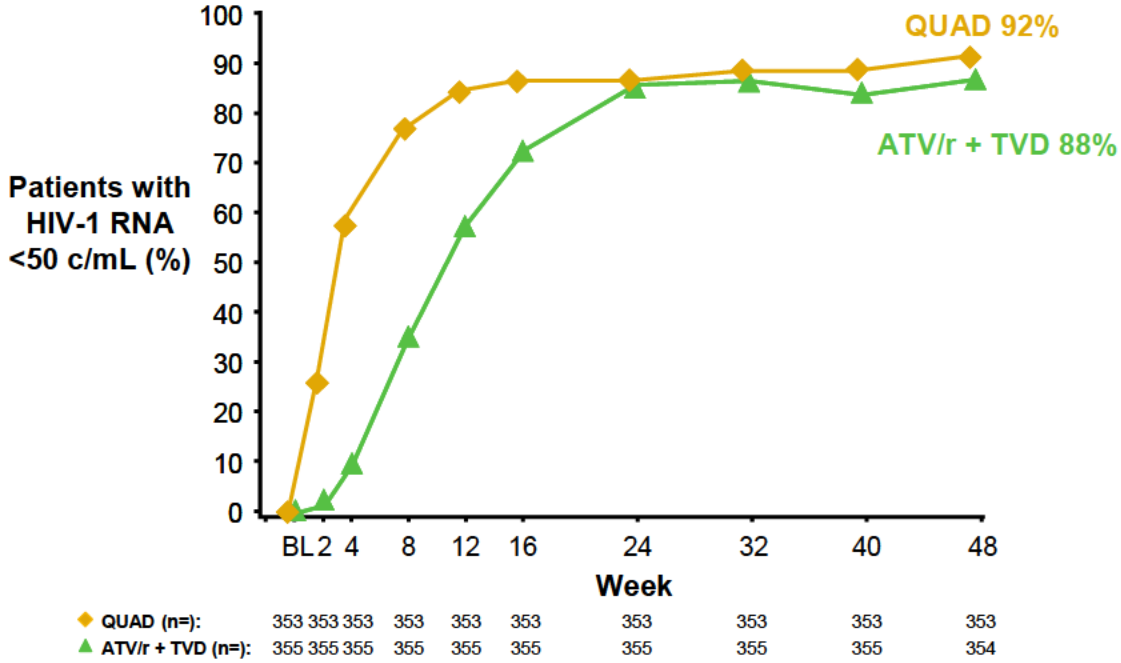
The FDA-defined TLOVR analysis results were consistent with the results of the snapshot analysis, confirming that the QUAD STR and ATV/r+TVD had comparable rates of virologic response. Based on the TLOVR analysis, 86.1% of subjects (304 of 353) in the QUAD group and 84.8% of subjects (301 of 355) in the ATV/r+TVD group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The difference in the percentages of responders at Week 48 was 1.6% (95% CI: –3.6% to 6.8%), which is consistent with the results of the primary endpoint analysis.

7.1.3.3. Tertiary Efficacy Endpoints

Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using M=F and M=E methods were similar between treatments. In the M=F analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was significantly greater in the QUAD group than in the ATV/r+TVD group from Week 2 through Week 16; response rates between the 2 groups were similar from Week 24 through Week 48. At Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 91.5% (323 of 353) in the QUAD group and 88.2% (313 of 355) in the ATV/r+TVD group (Figure 7). In the M=E analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 was 96.7% (323 of 334) in the QUAD group and 96.9% (313 of 323) in the ATV/r+TVD group.

Figure 7. **GS-US-236-0103: Subjects with HIV-1 RNA < 50 Copies/mL (M=F)**



ATV/r, ritonavir-boosted atazanavir; BL, baseline; M=F, missing = failure; TVD, Truvada

Change from Baseline in CD4 Cell Count

Mean (SD) baseline CD4 cell counts were 364 (180.6) cells/µL in the QUAD group and 375 (158.9) cells/µL in the ATV/r+TVD group. CD4 cell counts increased following administration of study drug, and the mean increases were similar between the QUAD and ATV/r+TVD groups at all time points. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 207 (164.2) cells/µL in the QUAD group and 211 (160.3) cells/µL in the ATV/r+TVD group. The difference in LSMs from an ANOVA model was –6 (95% CI: –31 to 18).

Table 14. GS-US-236-0103: Key Treatment Outcomes (ITT Analysis Set)

Treatment Outcomes	QUAD (N = 353)	ATV/r+TVD (N = 355)	QUAD vs ATV/r+TVD Difference in Percentages (95% CI)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis (n, %)[a]	316 (89.5%)	308 (86.8%)	3.0% (–1.9% to 7.8%)[b, c]
Virologic Responder (HIV-1 RNA < 50 copies/mL) at Week 48 using TLOVR Analysis (n, %)[a, d]	304 (86.1%)	301 (84.8%)	1.6% (–3.6% to 6.8%)[e]
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M=F) (n, %)[f]	323 (91.5%)	313 (88.2%)	3.5% (–1.0% to 8.0%)[e]
Mean (SD) Change from Baseline in CD4 cell count at Week 48 (cells/µL)	207 (164.2)	211 (160.3)	–6 (–31 to 18)[g]

ATV/r, ritonavir-boosted atazanavir; CD4, cluster of differentiation 4; CI, confidence interval; IDMC, independent data monitoring committee; ITT, intent-to-treat; LSM, least-squares mean; M=F, missing = failure; MH, Mantel-Haenszel; TLOVR, time to loss of virologic response; TVD, Truvada

a Week 48 window is between Day 309 and 378 (inclusive).

b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c At each of the 2 IDMC meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

d Responder refers to subjects who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.

e Difference in response rate (responder) and its 95% CI were from baseline HIV-1 RNA stratum-adjusted MH proportion.

f For the M=F analysis, denominator for percentage was the number of subjects in the ITT analysis set.

g The difference in LSMs and its 95% CI were computed adjusted for baseline HIV-1 RNA level.

7.1.4. Pooled Efficacy (GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103)

Pooling of the data was considered appropriate due to the similarity in study design and eligibility criteria of each of the studies. The primary efficacy endpoint for the pooled study data was the percentage of subjects with virologic success at Week 48 (HIV-1 RNA < 50 copies/mL) using the FDA-defined snapshot analysis algorithm.

Based on the pooled data from Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 (Table 15), the percentages of subjects having virologic success (ITT) at Week 48 were 88.8% (665 of 749 subjects) in the QUAD group; 84.0% (315 of 375 subjects) in the Atripla group (Studies GS-US-236-0104 and Studies GS-US-236-0102); and 86.8% (308 of 355 subjects) in the ATV/r+TVD group (Study GS-US-236-0103). The difference in percentages (5.1% [95% CI: 0.7% to 9.4%]) favored the QUAD group over the

Atripla group. The difference in the percentages between the QUAD group and the ATV/r+TVD group was 1.9% (95% CI: −2.3% to 6.1%).

Overall, 88.8% of subjects (665 of 749) in the pooled QUAD group (pooled GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103) and 85.3% of subjects (623 of 730) in the pooled control group (Atripla in GS-US-236-0104 and GS-US-236-0102, and ATV/r+TVD in GS-US-236-0103) had virologic success (ITT analysis set). The difference in percentages (3.5% [95% CI: 0.1% to 7.0%]) favored the pooled QUAD group over the pooled control group with the lower-bound of the 95% CI > 0 (Figure 8).

Reasons for VF or lack of virologic data in the Week 48 analysis window were balanced across the treatment groups.

Table 15. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Pooled Data for Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

	QUAD	ATR	ATV/r+TVD
	236-0104, 0102, 0103 (N = 749)	236-0104, 0102 (N = 375)	236-0103 (N = 355)
Virologic Success at Week 48[a]			
HIV-1 RNA < 50 copies/mL	665 (88.8%)	315 (84.0%)	308 (86.8%)
QUAD vs ATR			
Difference in Percentages[b]	5.1%		
95% CI[b]	0.7% to 9.4%		
QUAD vs ATV/r+TVD			
Difference in Percentages[b]	1.9%		
95% CI[b]	(–2.3% to 6.1%)		
Virologic Failure at Week 48	48 (6.4%)	28 (7.5%)	19 (5.4%)
HIV-1 RNA ≥ 50 copies/mL	21 (2.8%)	12 (3.2%)	8 (2.3%)
Discontinued Study Drug Due to Lack of Efficacy	8 (1.1%)	2 (0.5%)	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c]	19 (2.5%)	14 (3.7%)	11 (3.1%)
No Virologic Data in Week 48 Window	36 (4.8%)	32 (8.5%)	28 (7.9%)
Discontinued Study Drug Due to AE/Death	21 (2.8%)	20 (5.3%)	18 (5.1%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	15 (2.0%)	11 (2.9%)	9 (2.5%)
Missing Data during Window but on Study Drug	0	1 (0.3%)	1 (0.3%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; MH, Mantel-Haenszel; TVD, Truvada

a Week 48 window is between Day 309 and 378 (inclusive).

b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

7.1.5. Comparison of Results in Subpopulations

The primary analysis of virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis algorithm, ITT analysis set) was analyzed for age (< 40 and ≥ 40 years), sex, and race (white and nonwhite) in accordance with ICH M4E guidance. Virologic response was also analyzed by baseline HIV-1 RNA level (≤ 100,000 and > 100,000 copies/mL) and baseline CD4 cell counts (≤ 350 and > 350 cells/μL), which are widely accepted surrogate markers of HIV disease severity.

Subgroup analyses revealed high and generally comparable rates of virologic success in the QUAD and control groups with those observed for the overall study population, with point estimates mostly favoring the QUAD group, as seen in the overall population and across various efficacy endpoint analyses (Figure 8).

None of the 3 studies were powered for individual subgroup analyses. Subgroup analyses results from Study GS-US-236-0104 were not prespecified in the SAPs for the study because of the small sample size. However, data from Study GS-US-236-0104 were included in the prespecified pooled analysis to improve precision because the sample sizes in some subgroups (eg, women) were small. Subgroup analyses results from Studies GS-US-236-0102 and GS-US-236-0103 were prespecified in the study SAPs and are therefore presented in addition to the pooled data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103.

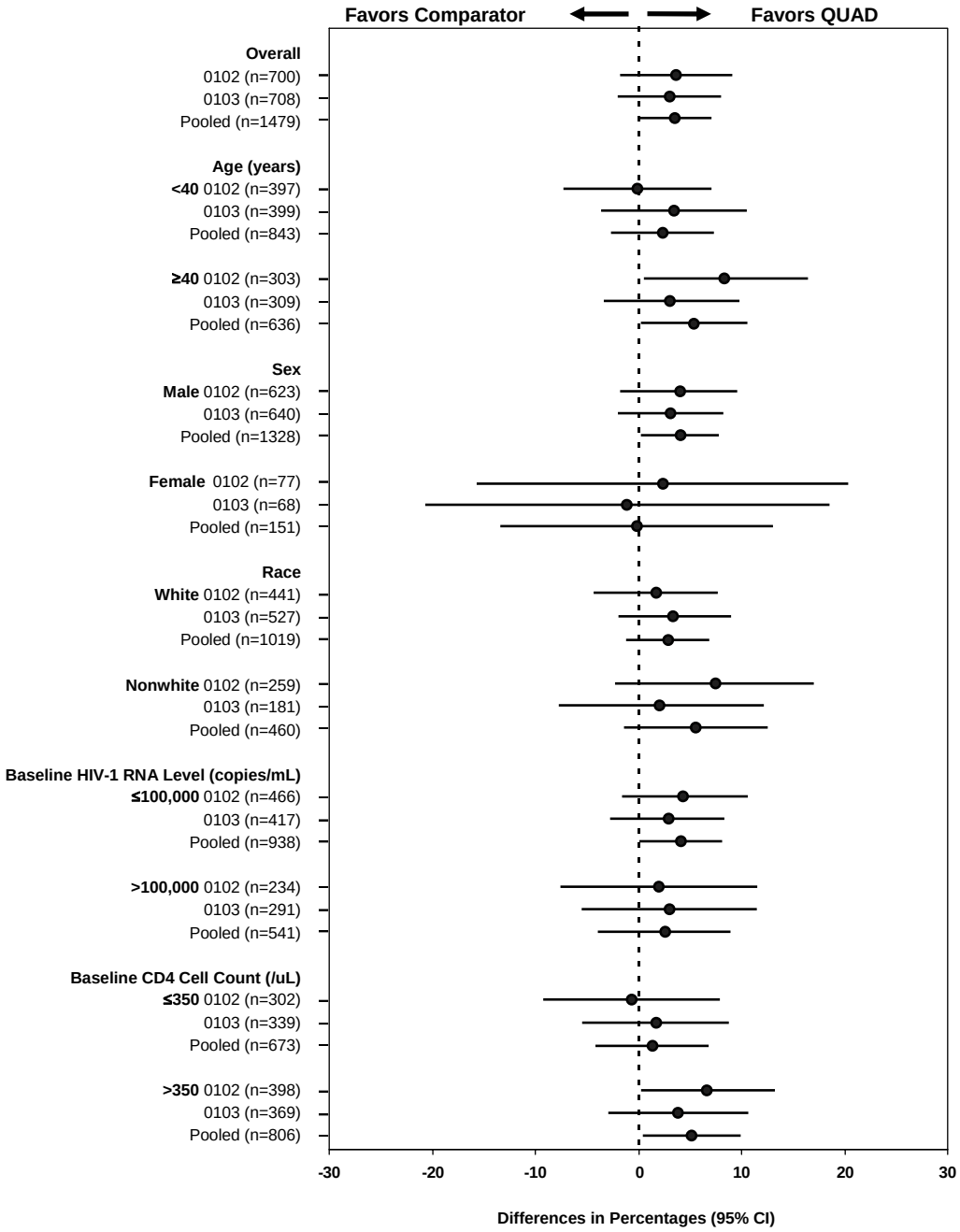
Homogeneity tests of the treatment effects between subgroups were performed for individual and pooled study data for virologic success at Week 48 (HIV-1 RNA < 50 copies/mL, snapshot analysis). There were no significant differences in treatment effects between subgroups.

Additional adhoc analyses were performed on Study GS-US-236-0103 on the treatment difference in virologic success by region at Week 48 (GS-US-236-0104 and GS-US-236-0102 were conducted in the US only). In the QUAD group, 92.3% of the non-US subjects and 87.3% of the US subjects had HIV-1 RNA < 50 copies/mL at Week 48. In the ATV/r+TVD group, 90% of the non-US subjects and 83.8% of the US subjects had HIV-1 RNA < 50 copies/mL at Week 48 (Table 16).

Table 16. Study GS-US-236-0103: Treatment Difference in Virologic Success by Region at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

Region	QUAD	ATV/r+TVD	Difference in Percentages (95% CI)
Non-US	144/156 (92.3%)	153/170 (90.0%)	2.3% (–4.0%, 8.6%)
US	172/197 (87.3%)	155/185 (83.8%)	4.1% (–3.0%, 11.2%)

Figure 8. **Individual Studies GS-US-236-0102 and GS-US-236-0103 and Pooled Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis, ITT Analysis Set)**



CD, cluster of differentiation 4; CI, confidence interval; ITT, intent-to-treat; MH, Mantel-Haenszel

Difference in response rate and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (if it is not the subgroup factor) and study (for pooled analysis).

Pooled data are for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103.

7.2. Summary of Clinical Resistance Findings

HIV-1 isolates with reduced susceptibility to each of the individual antiviral agents of the QUAD STR have been selected in vitro. HIV-1 isolates that have been identified from subjects with VF have reduced susceptibility to 1 or more components of the QUAD STR.

Between EVG, FTC, and TFV, no substantial cross-resistance to EVG or TFV has been demonstrated with the FTC-selected M184V/I mutation. In vitro cross-resistance to FTC has been shown with the TFV-selected K65R mutation, but there was no cross-resistance to EVG. EVG retains potent antiviral activity against HIV-1 with drug resistance mutations of the NNRTI, NRTI, and PI classes.

A summary of the principal resistance data relevant to the use of the QUAD STR is provided in this section.

7.2.1. Established Resistance Profiles

In vitro resistance selection experiments with EVG demonstrated that EVG can select 3 primary resistance mutations in HIV-1 IN, the T66I, E92Q, or Q148R mutations. The T66I, E92Q, and Q148R mutations resulted in HIV-1 that had 15-, 36-, and 109-fold reduced susceptibility to EVG, respectively. EVG showed cross-resistance in vitro to the RAL-selected mutations T66A/K, Q148H/K, and N155H. The other integrase mutations H51Y, F121Y, S147G, S153Y, E157Q, and R263K were also selected by EVG and further decreased susceptibility to EVG when added to either the T66I or E92Q mutations.

7.2.2. Clinical Resistance Findings for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

This section describes data for HIV-1 infected antiretroviral treatment-naive subjects who met resistance analysis criteria in the randomized, double-blind treatment periods in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103. The protease/reverse transcriptase (PR/RT) genotype was assessed in subjects at screening. Resistance analyses were performed on plasma HIV-1 isolates from all subjects with confirmed VF or HIV-1 RNA > 400 copies/mL at Week 48 (Week 60 in Study GS-US-236-0104) or at the time of early study drug discontinuation. Resistance development to 1 or more components of the QUAD STR, Atripla, or ATV/r+TVD occurred infrequently in these studies. Of the 1479 randomized and treated subjects across the 3 studies, 53 subjects (3.6%) were included in the resistance analysis population and were analyzed for resistance development.

In the pooled QUAD group, 27 subjects were analyzed for resistance development (27 of 749 subjects, 3.6%). Thirteen subjects (13 of 749 subjects, 1.7%) in the QUAD group developed primary integrase or NRTI resistance mutations (most commonly T66I [n = 2], E92Q [n = 8], Q148R [n = 3], and N155H [n = 3] in the integrase gene, and M184V/I [n = 12], with or without K65R [n = 4], in the RT gene) and phenotypic resistance to 1 or more components of the QUAD STR. Other INSTI mutations (secondary integrase mutations) that developed, each in a single case in addition to a primary INSTI mutation, were H51Y, L68V, G140C, S153A, and E157Q. Within the QUAD group, subjects who

developed genotypic resistance to EVG (n = 11) showed a mean of ≥ 67-fold reduced susceptibility to EVG compared with wild-type. All subjects who developed resistance to EVG also showed reduced susceptibility to RAL (mean 7.9-fold) (see Appendix 4 for a pooled listing of subjects with emergent HIV-1 resistance at Week 48).

The majority of subjects across these 3 studies were infected with subtype B HIV-1 (94.7%). Among those infected with non-B HIV-1 subtypes in the QUAD group, no impact of HIV-1 subtype on response or development of resistance was observed. Subjects in the QUAD group and included in the resistance analysis population, as well as those who developed mutations, had a trend for higher baseline viral load and lower CD4 cell count than the overall study population, indicative of more advanced HIV disease. Overall, a trend for lower HIV-1 replication capacity in vitro was found in subjects who developed resistance to a component of the QUAD STR compared with baseline.

In Study GS-US-236-0103, 27 subjects in the QUAD group had the NNRTI-associated K103N substitution in RT at baseline; none of these subjects developed resistance to any components of the QUAD STR. The presence of K103N at baseline did not predispose subjects to failure on the QUAD STR or ATV/r+TVD. No subjects from GS-US-236-0102 had K103N, as required by the protocol. In Studies GS-US-236-0102 and GS-US-236-0103, 18 subjects had primary PI-associated resistance mutations at baseline (3 with reduced susceptibility to ATV, but all were susceptible to ATV/r, meeting entry criteria for the study); none of these subjects developed resistance to any components of the QUAD STR.

Phenotypic resistance data were available for 26 subjects receiving the QUAD STR, 11 of 749 (1.5%) subjects had reduced susceptibility to EVG, 12 of 749 (1.6%) subjects had reduced susceptibility to FTC, and 2 of 749 (0.3%) subjects had reduced susceptibility to TFV. Substantial cross-resistance was observed between EVG and RAL, and between FTC and 3TC. These subject isolates remained susceptible to common second-line treatment regimens consisting of PIs, NNRTIs, and most other NRTIs.

Overall, resistance development to 1 or more components of the QUAD STR, Atripla, or ATV/r+TVD occurred infrequently in these studies (1.7% of subjects in the QUAD group, 2.1% of subjects in the Atripla group, and no subjects in the ATV/r+TVD group). The most common emergent HIV-1 resistance mutations in the QUAD group were T66I, E92Q, Q148R, and N155H in the integrase gene, and M184V/I and K65R in the RT gene. The resistance profile observed with the QUAD STR reflected the resistance profiles observed for the individual components of this STR.

7.3. Efficacy Discussion and Conclusions

In Phase 3 Studies GS-US-236-0102 and GS-US-236-0103, results from the primary efficacy analysis using the FDA-defined snapshot algorithm demonstrated that QUAD once daily was noninferior to the control group (GS-US-236-0102: 88% of subjects in the QUAD group and 84% of subjects in the Atripla group had virologic success [HIV-1 RNA < 50 copies/mL]; GS-US-236-0103: 90% of subjects in the QUAD group and 87% of subjects in the

ATV/r+TVD group had virologic success) when administered for 48 weeks to HIV-1 infected, antiretroviral treatment-naive adults.

The virologic success rate of the standard-of-care comparators was higher than results seen in previous studies. In Study GS-US-236-0102, the virologic success rate in the Atripla group for the primary endpoint was higher than has been observed in prior studies {17599}. The virologic success rate in Study GS-US-236-0103 was consistent or higher than that observed in other prior studies with ATV/r+TVD {14695}, {12302}, {18498}. There are several potential explanations for these findings, including a higher baseline CD4 cell count in subjects, indicating earlier diagnosis and treatment of HIV-1 infection. In addition, Study GS-US-236-0102 was the first head-to-head Phase 3 study where the Atripla STR was used as the comparator in treatment-naive subjects. The high response rates observed in the control groups for these studies established the efficacy of the QUAD STR against highly active comparators that are preferred and recommended regimens for antiretroviral treatment-naive subjects per US DHHS and European AIDS Clinical Society (EACS) HIV Treatment Guidelines, respectively {20239}, {18917}.

In the pooled data for GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, the following subgroups had point estimates that favored QUAD over Atripla, with the lower-bound of the 95% CI > 0: age ≥ 40 years, male subjects, baseline HIV-1 RNA ≤ 100,000 copies/mL, and baseline CD4 cell count > 350 cells/µL.

In Studies GS-US-236-0102 and GS-US-236-0103, the secondary endpoint analysis using the FDA-defined TLOVR algorithm confirmed the results of the snapshot analysis, with a comparable response (achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48) to QUAD compared with control (GS-US-236-0102: 86% of subjects in the QUAD group and 83% of subjects in the Atripla group; GS-US-236-0103: 86.1% of subjects in the QUAD group and 84.8% of subjects in the ATV/r+TVD group). Analyses of tertiary HIV-1 RNA endpoints provided further robustness to the efficacy analysis by demonstrating comparable response rates to QUAD compared with control at Week 48.

Following study drug administration, HIV-1 RNA levels decreased more rapidly in the QUAD group compared with the control groups at the earlier time points (GS-US-236-0104: Week 2 through Week 8; GS-US-236-0102: Week 2 through Week 8 [Figure 6]; GS-US-236-0103: Week 2 through Week 12, [Figure 7]) and were similar between the QUAD and control groups through Week 48. The rapid time to virologic suppression with the QUAD STR is consistent with the potency of HIV integrase inhibitors {12208}.

In Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, immunologic benefits of treatment with QUAD and control were demonstrated by improvements in CD4 cell counts in both groups through Week 48 (Week 60 in Study GS-US-236-0104).

PK/PD analyses for efficacy demonstrate high rates of virologic response across the range of clinically observed EVG trough concentrations.

In the pooled resistance analysis for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, the development of 1 or more primary EVG, FTC, or TFV resistance-associated substitution were observed in 13 of the 26 subjects with evaluable genotypic data from paired baseline and QUAD treatment-failure isolates (1.7%, 13 of 749 subjects). The most common substitutions that emerged were T66I, E92Q, Q148R, and N155H in IN, and M184V/I and K65R in RT. Phenotypic resistance data were available for 26 subjects receiving QUAD as follows: 11 of 749 (1.5%) subjects had reduced susceptibility to EVG; 12 of 749 (1.6%) subjects had reduced susceptibility to FTC; and 2 of 749 (0.3%) subjects had reduced susceptibility to TFV.

In conclusion, the QUAD STR has demonstrated high rates of virologic success in Phase 2 Study GS-US-236-0104 and Phase 3 Studies GS-US-236-0102 and GS-US-236-0103, and noninferiority to preferred antiretroviral regimens. The efficacy results of the QUAD STR were confirmed by multiple sensitivity and subgroup analyses. Taken together, these data highlight the potent and durable efficacy profile of the QUAD STR versus highly active comparators for the treatment of treatment-naive, HIV-1 infected subjects.

8. SAFETY

The safety profiles of EVG and COBI are derived from clinical studies with these individual agents. The clinical safety of the individual components FTC and TDF, in combination with other antiretroviral agents, has been established in both treatment-naive and treatment-experienced subjects (refer to US prescribing information for Emtriva: {12644}, Viread: {16282}, and Truvada: Appendix 1). The safety of the QUAD STR in HIV-1 infected subjects is derived from the profiles of each component, the in-depth and comprehensive QUAD clinical development program, and the extensive clinical and postmarketing experience with the FTC and TDF components of the QUAD STR.

In addition to individual study safety data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, pooled safety data up to the Week 48 cutoff dates (Week 60 for Study GS-US-236-0104) are presented. Individual study findings are presented for appropriate safety endpoints for which pooling was not performed. Supportive safety data are provided from additional studies of EVG, COBI, and the QUAD STR. Data from the QUAD Safety Update are presented in Section 8.18.

8.1. Phase 1 Safety

In the Phase 1 clinical studies conducted in healthy subjects, the QUAD STR was generally well tolerated at 2 dose levels of COBI (100 and 150 mg). Most reported AEs were mild (Grade 1) or moderate (Grade 2) in severity and resolved without treatment. Frequently reported treatment-emergent AEs (≥ 10% of subjects per treatment group and at least 2 subjects per treatment group) in healthy subjects who received the QUAD STR included nausea, abdominal pain, vomiting, diarrhea, anorexia, headache, dizziness, nasal congestion, and fatigue.

No deaths occurred in the Phase 1 QUAD STR studies. One SAE was reported; in Study GS-US-236-0101, 1 subject experienced acute appendicitis (Grade 3), which was considered to be an SAE and led to the subject being discontinued from the study. The event was assessed as not related to study drug.

8.2. Extent of Exposure for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

In Study GS-US-236-0104, the median (first quartile [Q1]–third quartile [Q3]) duration of exposure to study drug was 58.4 (57.0–60.0) weeks in the QUAD group (N = 48) and 58.9 (57.0–59.7) weeks in the Atripla group (N = 23).

In Study GS-US-236-0102, the median (Q1–Q3) duration of exposure to study drug was 59.3 (48.1–60.1) weeks in the QUAD group (N = 348) and 57.9 (48.0–60.1) weeks in the Atripla group (N = 352).

In Study GS-US-236-0103, the median (Q1–Q3) duration of exposure to study drug was 48.1 (46.1–50.1) weeks in the QUAD group (N = 353) and 48.1 (46.1–51.0) weeks in the ATV/r+TVD group (N = 355).

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, 749 subjects received QUAD, 375 subjects received Atripla, and 355 subjects received ATV/r+TVD. The median (Q1–Q3) duration of exposure to study drug was 48.4 (47.9–60.0) weeks in the QUAD group, 58.9 (48.1–60.1) weeks in the Atripla group, and 48.1 (46.1–51.0) weeks in the ATV/r+TVD group. Median exposure to study drug was generally similar within each study, but the shorter exposure in Study GS-US-236-0103 led to smaller median exposure in the pooled QUAD and ATV/r+TVD groups compared with the Atripla group in the pooled analysis (interquartile ranges for exposure were similar in the pooled QUAD group and in the Atripla group).

8.3. Safety in Study GS-US-236-0104

There were no marked differences between treatment groups in the duration of exposure to study drug in the randomized phase (median [Q1–Q3] exposure was 58.4 [57.0–60.0] weeks in the QUAD group and 58.9 [57.0–59.7] weeks in the Atripla group).

The STRs of QUAD and Atripla were well tolerated in this study. No subjects died during this study. In the randomized phase, similar percentages of subjects in each group reported any SAE (QUAD 4.2%, 2 subjects; Atripla 4.3%, 1 subject) or any AE (QUAD 91.7%, 44 subjects; Atripla 91.3%, 21 subjects). Lower percentages of subjects in the QUAD group compared with the Atripla group reported any AE considered related to study drug by the investigator (QUAD 47.9%, 23 subjects; Atripla 56.5%, 13 subjects); any Grade 2, 3, or 4 AE (QUAD 45.8%, 22 subjects; Atripla 56.5%, 13 subjects); any Grade 2, 3, or 4 AE considered related to study drug by the investigator (QUAD 14.6%, 7 subjects; Atripla 26.1%, 6 subjects); or any Grade 3 or 4 AE (QUAD 4.2%, 2 subjects; Atripla 8.7%, 2 subjects). No SAEs or Grade 3 or 4 AEs were considered related to study drug by the investigator in the randomized phase. One subject in the Atripla group discontinued study drug due to an AE in the randomized phase (suicidal ideation, considered related to study drug by the investigator).

In the randomized phase, the most frequently reported AEs were as follows:

- QUAD group — diarrhea (27.1%, 13 subjects), fatigue (16.7%, 8 subjects), and headache (14.6%, 7 subjects)

- Atripla group — abnormal dreams (34.8%, 8 subjects), upper respiratory tract infection (26.1%, 6 subjects), and sinusitis (21.7%, 5 subjects)

The majority of the AEs reported in the study were mild (Grade 1) or moderate (Grade 2) in severity.

Important AEs to aid comparison between QUAD and Atripla were selected neurological and psychiatric events, and selected rash events. A lower percentage of subjects in the QUAD

group compared with the Atripla group reported important neurological and psychiatric AEs (QUAD 41.7%, 20 subjects; Atripla 56.5%, 13 subjects). Abnormal dreams, anxiety, and dizziness were each reported for a lower percentage of subjects in the QUAD group than in the Atripla group. A lower percentage of subjects in the QUAD group compared with the Atripla group reported important rash AEs (QUAD 18.8%, 9 subjects; Atripla 26.1%, 6 subjects). Rash (preferred term [PT]) was reported for a lower percentage of subjects in the QUAD group than in the Atripla group.

There were no clinically relevant changes from baseline in median values for hematology, clinical chemistry, fasting lipid, thyroid stimulating hormone (TSH), or immunoglobulin parameters in either group during the randomized phase.

In the randomized phase for the QUAD group, there was a small increase in serum creatinine (baseline median 0.88 mg/dL; Week 60 median change from baseline 0.17 mg/dL) and a small decrease in $eGFR_{CG}$ (baseline median 120.7 mL/min; Week 60 median change from baseline −17.4 mL/min). These changes were seen as early as Week 2, but they were stable and nonprogressive beyond Week 24, and median values remained within the normal range. No subjects had $eGFR_{CG}$ below 50 mL/min during the study. No clinically relevant changes were seen in the Atripla group. No clinically relevant changes in serum phosphorus were seen in either group.

There were no clinically relevant changes in median values for body weight or ECG parameters.

8.4. Safety in Study GS-US-236-0102

A summary of AE categories is provided in Table 17. The STRs of QUAD and Atripla were well tolerated in this study through a median duration of study drug exposure of 59.3 weeks in the QUAD group and 57.9 weeks in the Atripla group. The percentages of subjects with any AE (QUAD 94.0%, 327 subjects; Atripla 94.9%, 334 subjects), any Grade 2, 3, or 4 AE (QUAD 54.9%, 191 subjects; Atripla 54.8%, 193 subjects), or any Grade 3 or 4 AE (QUAD 12.9%, 45 subjects; Atripla 11.1%, 39 subjects) were similar between the 2 groups. Most clinical AEs reported in either treatment group were mild (Grade 1) or moderate (Grade 2) in severity.

Three subjects died during the study (1 death [suicide] in the QUAD group and 2 deaths [1 due to suicide considered related to study drug and 1 due to metastatic carcinoma] in the Atripla group). Serious AEs were reported for a higher percentage of subjects in the QUAD group compared with the Atripla group (QUAD 11.8%, 41 subjects; Atripla 6.8%, 24 subjects). Serious AEs considered by the investigator to be related to study drug were infrequent in both treatment groups (QUAD 0.9%, 3 subjects; Atripla 2.0%, 7 subjects). Thirty-one subjects discontinued study drug due to an AE (QUAD 3.7%, 13 subjects; Atripla 5.1%, 18 subjects). Centers for Disease Control Class C AIDS-defining events were reported for a similar percentage of subjects in both treatment groups (QUAD 1.1%, 4 subjects; Atripla 0.3%, 1 subject). Lower percentages of subjects in the QUAD group compared with

the Atripla group reported AEs considered by the investigator to be related to study drug (QUAD 46.3%, 161 subjects; Atripla 67.3%, 237 subjects).

Table 17. GS-US-236-0102: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

Adverse Event Category, n (%)	QUAD (N = 348)	ATR (N = 352)
Subjects Experiencing Any Treatment-Emergent AE	327 (94.0%)	334 (94.9%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE	45 (12.9%)	39 (11.1%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	161 (46.3%)	237 (67.3%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related AE	11 (3.2%)	15 (4.3%)
Subjects Experiencing Any Treatment-Emergent SAE	41 (11.8%)	24 (6.8%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related SAE	3 (0.9%)	7 (2.0%)
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	13 (3.7%)	18 (5.1%)
Subjects who had Treatment-Emergent Death[a]	1 (0.3%)	2 (0.6%)

AE, adverse event; ATR, Atripla; SAE, serious adverse event

a Treatment-emergent death refers to deaths occurring between the first dose date and the last dose date plus 30 days (inclusive).

The most frequently reported AEs in either treatment group were diarrhea (QUAD 23.0%; 80 subjects, Atripla 18.8%, 66 subjects); nausea (QUAD 20.7%, 72 subjects; Atripla 13.6%, 48 subjects); abnormal dreams (QUAD 15.2%, 53 subjects, Atripla 27.0%, 95 subjects); and dizziness (QUAD 6.6%, 23 subjects; Atripla 24.4%, 86 subjects).

Prespecified AEs of interest for the QUAD STR (renal events and bone fractures) occurred infrequently in both the QUAD and Atripla treatment groups (fracture events: 1.7%, 6 subjects for each treatment group [p = 1.00]; renal events: QUAD 1.4%, 5 subjects and Atripla 0.3%, 1 subject [p = 0.12]). Fractures typically occurred in the extremities, and all were due to traumatic injury.

Selected neurological and psychiatric events and selected rash events were predefined in this study as important AEs to aid comparison between QUAD and Atripla. The overall percentages of these important AEs were lower in the QUAD group compared with the Atripla group (neurological and psychiatric events: QUAD 42.8%, 149 subjects and Atripla 62.5%, 220 subjects; rash events: QUAD 17.0%, 59 subjects and Atripla 27.8%, 98 subjects).

Mean increases from baseline through Week 48 in fasting total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol were lower for the QUAD group compared with the Atripla group (in ad hoc testing: total cholesterol $p < 0.001$, LDL and HDL cholesterol each $p = 0.001$). Renal laboratory assessments showed changes consistent with

COBI administration (effect on eGFR). Specifically, there was a small increase in serum creatinine (median change from baseline at Week 48: 0.14 mg/dL) and corresponding small decreases in $eGFR_{CG}$ or eGFR calculated using the Modification of Diet in Renal Disease equation ($eGFR_{MDRD}$) (~10%–15% change from baseline) in the QUAD group. Changes in $eGFR_{CG}$ and $eGFR_{MDRD}$ were seen as early as Week 2, after which they generally stabilized by Week 24 and were nonprogressive through Week 48. No other clinically relevant changes from baseline in median values for hematology or clinical chemistry were observed.

Most subjects had at least 1 treatment-emergent laboratory abnormality reported during the study (QUAD 92.5%, 321 subjects; Atripla 91.7%, 322 subjects). The majority of the abnormalities reported were Grade 1 or 2 in severity. Treatment-emergent Grade 3 or 4 abnormalities were reported less frequently in the QUAD group than in the Atripla group (QUAD 17.0%, 59 subjects; Atripla 23.4%, 82 subjects). Liver enzyme abnormalities (ALT, AST, gamma-glutamyltransferase [GGT], and alkaline phosphatase) occurred in a lower percentage of subjects in the QUAD group than in the Atripla group.

There were no clinically relevant changes in median values for body weight and no notable differences between treatment groups in the percentages of subjects with ECG abnormalities.

8.5. Safety in Study GS-US-236-0103

A summary of AE categories is provided in Table 18. The QUAD STR and the ATV/r+TVD regimen were well tolerated in this study through a median duration of study drug exposure of 48.1 weeks in both treatment groups. The percentages of subjects with any AE (QUAD 91.5%, 323 subjects; ATV/r+TVD 93.8%, 333 subjects), any Grade 2, 3, or 4 AE (QUAD 56.9%, 201 subjects; ATV/r+TVD 62.0%, 220 subjects), or any Grade 3 or 4 AE (QUAD 12.7%, 45 subjects; ATV/r+TVD 13.5%, 48 subjects) were similar between the 2 groups. Most clinical AEs reported in either treatment group were mild (Grade 1) or moderate (Grade 2) in severity.

Three subjects died during the study (due to septic shock, *Pneumocystis carinii* pneumonia, and cardiopulmonary arrest); all deaths were in the ATV/r+TVD group. Serious AEs were reported for a lower percentage of subjects in the QUAD group compared with the ATV/r+TVD group (QUAD 7.4%, 26 subjects; ATV/r+TVD 8.7%, 31 subjects). The SAEs considered by the investigator to be related to study drug were balanced and infrequent in both treatment groups (0.6% [2 subjects] in each treatment group). Thirty-one subjects discontinued study drug due to an AE (QUAD 3.7%, 13 subjects; ATV/r+TVD 5.1%, 18 subjects). Centers for Disease Control Class C AIDS-defining events were reported for a similar percentage of subjects in both treatment groups (QUAD 0.8%, 3 subjects; ATV/r+TVD 2.0%, 7 subjects). Lower percentages of subjects in the QUAD group compared with the ATV/r+TVD group reported AEs considered by the investigator to be related to study drug (QUAD 45.0%, 159 subjects; ATV/r+TVD 57.2%, 203 subjects).

Table 18. GS-US-236-0103: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

Adverse Event Category, n (%)	QUAD (N = 353)	ATV/r+TVD (N = 355)
Subjects Experiencing Any Treatment-Emergent AE	323 (91.5%)	333 (93.8%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE	45 (12.7%)	48 (13.5%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related AE	159 (45.0%)	203 (57.2%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related AE	9 (2.5%)	13 (3.7%)
Subjects Experiencing Any Treatment-Emergent SAE	26 (7.4%)	31 (8.7%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related SAE	2 (0.6%)	2 (0.6%)
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	13 (3.7%)	18 (5.1%)
Subjects who had Treatment-Emergent Death[a]	0	3 (0.8%)

AE, adverse event; ATV/r, ritonavir-boosted atazanavir; SAE, serious adverse event; TVD, Truvada

a Treatment-emergent death refers to deaths occurring between the first dose date and the last dose date plus 30 days (inclusive).

The most frequently reported AEs in both treatment groups were diarrhea (QUAD 21.8%, 77 subjects; ATV/r+TVD 27.3%, 97 subjects); nausea (QUAD 19.8%, 70 subjects; ATV/r+TVD 19.4%, 69 subjects); and upper respiratory tract infection (QUAD 15.3%, 54 subjects; ATV/r+TVD 16.3%, 58 subjects).

Prespecified AEs of interest for the QUAD STR were renal events and bone fractures. No prespecified renal events occurred in either treatment group; fractures occurred infrequently in both the QUAD and the ATV/r+TVD groups (fracture events: QUAD 0.8%, 3 subjects; ATV/r+TVD 1.7%, 6 subjects). The majority of fractures (7 of 9 subjects) were due to traumatic injury. Two subjects experienced nontraumatic bone fractures, 1 in each treatment group (the subject in the QUAD group had a bilateral fracture of the calcaneus and the subject in the ATV/r group had a vertebral fracture of T9).

Selected rash events were predefined in this study as important AEs to aid comparison between QUAD and ATV/r+TVD. The overall percentages of these important AEs were similar in the QUAD group compared with the ATV/r+TVD group (QUAD 17.8%, 63 subjects; ATV/r+TVD 18.0%, 64 subjects).

Mean increases from baseline through Week 48 in fasting triglycerides were lower for the QUAD group compared with the ATV/r+TVD group ($p = 0.006$). Mean increases from baseline through Week 48 in other metabolic parameters (ie, fasting total cholesterol, LDL and HDL cholesterol) were similar for the QUAD group compared with the ATV/r+TVD group. Renal laboratory assessments showed a small increase in serum creatinine (median change from baseline at Week 48 was 0.12 mg/dL in the QUAD group and 0.08 mg/dL in the

ATV/r+TVD group) and corresponding small decreases in $eGFR_{CG}$ (median change from baseline −12.7 mL/min in the QUAD group and −9.5 mL/min in the ATV/r+TVD group). Changes in $eGFR_{CG}$ were seen as early as Week 2, after which they generally stabilized by Week 8 and were nonprogressive through Week 48.

Most subjects had at least 1 treatment-emergent laboratory abnormality reported during the study (QUAD 84.4%, 297 subjects; ATV/r+TVD 98.9%; 348 subjects). The majority of the abnormalities reported were Grade 1 or 2 in severity in the QUAD group and Grade 3 in the ATV/r+TVD group. Treatment-emergent Grade 3 or 4 laboratory abnormalities were reported less frequently in the QUAD group than in the ATV/r+TVD group (QUAD 16.2%, 57 subjects; ATV/r+TVD 67.9%; 239 subjects). Liver enzyme elevations in ALT and AST occurred in a lower percentage of subjects in the QUAD group compared with the ATV/r+TVD group (ALT: QUAD 15.3%, 54 subjects; ATV/r+TVD 21.6%, 76 subjects and AST: QUAD 17.6%, 62 subjects; ATV/r+TVD 21.9%; 77 subjects); abnormalities in GGT and alkaline phosphatase occurred in a similar percentage of subjects in both treatment groups. Total bilirubin abnormalities were lower in the QUAD group than in the ATV/r+TVD group (QUAD 3.1%, 11 subjects; ATV/r+TVD 96.3%; 339 subjects). No subjects in the QUAD group, and 14 subjects in the ATV/r+TVD group, had elevations in AST or ALT 3 times the upper limit of the normal range (ULN) along with elevations of serum bilirubin of 2 times the ULN.

Two subjects in the QUAD group with normal ECGs at baseline had developed clinically significant abnormal ECGs by Week 48; 1 subject in the ATV/r+TVD group with a nonclinically significant ECG abnormality at baseline developed a clinically significant abnormality by Week 48. No subjects had concomitant AEs at the time of the abnormal ECG findings. There were no clinically relevant changes in median values for body weight.

There were numerically lower mean percentage decreases from baseline in BMD at the lumbar spine and hip in the QUAD group compared with the ATV/r+TVD group (changes at Week 48: spine –2.63% in the QUAD group vs –3.33% in the ATV/r+TVD group; hip –3.06% in the QUAD group vs –3.88% in the ATV/r+TVD group); however, the differences between groups were not statistically significant.

8.6. Pooled AE and Clinical laboratory Safety Data (GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103)

8.6.1. Adverse Events

A brief summary of AEs reported in the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 is provided in Table 19. Similar percentages of subjects in each group reported any AE. While the overall incidences of treatment-emergent death, SAEs, or study drug discontinuation due to AEs were low, a higher percentage of subjects in the QUAD group compared with the Atripla group experienced SAEs (QUAD 9.2%, 69 subjects; Atripla 6.7%, 25 subjects), and a lower percentage of subjects in the QUAD group compared with the Atripla and ATV/r+TVD

groups discontinued due to an AE (QUAD 3.5%, 26 subjects; Atripla 5.1%, 19 subjects; ATV/r+TVD 5.1%, 18 subjects). Other notable differences between groups were as follows:

- A lower percentage of subjects in the QUAD group compared with the Atripla group and the ATV/r+TVD group reported any AE considered related to study drug by the investigator (QUAD 45.8%, 343 subjects; Atripla 66.7%, 250 subjects; ATV/r+TVD 57.2%, 203 subjects).

- A lower percentage of subjects in the QUAD group compared with the Atripla group reported any Grade 2, 3, or 4 AE considered related to study drug by the investigator (QUAD 13.0%, 97 subjects; Atripla 26.1%, 98 subjects).

- A lower percentage of subjects in the QUAD group compared with the ATV/r+TVD group reported any Grade 2, 3, or 4 AE (QUAD 55.3%, 414 subjects; ATV/r+TVD 62.0%, 220 subjects).

The most frequently reported AEs were as follows (Table 20):

- QUAD group — diarrhea (22.7%, 170 subjects), nausea (19.5%, 146 subjects), and headache (14.6%, 109 subjects)

- Atripla group — abnormal dreams (27.5%, 103 subjects), dizziness (23.7%, 89 subjects), and diarrhea (18.7%, 70 subjects)

- ATV/r+TVD group — diarrhea (27.3%, 97 subjects), nausea (19.4%, 69 subjects), and upper respiratory tract infection (16.3%, 58 subjects)

Subgroup analyses of AEs were performed by sex, age, race, HIV-1 stratum at baseline, and CD4 cell count at baseline. Overall, no differences between subgroups were apparent in the pattern of AEs reported; however, relatively few females were enrolled in the clinical studies, thereby limiting the interpretation of safety findings.

No relevant exposure-AE trends were observed in PK/PD analyses of the most frequently reported AEs; exposures (AUC_{tau} or C_{max}) to EVG, COBI, FTC, or TFV were comparable regardless of the presence/absence of headache, nausea, or diarrhea.

Table 19. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Overall Summary of Treatment-Emergent Adverse Events (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103 (N = 749)	ATR 236-0104, 0102 (N = 375)	ATV/r+TVD 236-0103 (N = 355)
Subjects Experiencing Any Treatment-Emergent AE	694 (92.7%)	355 (94.7%)	333 (93.8%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE	92 (12.3%)	41 (10.9%)	48 (13.5%)
Subjects Experiencing Any Study-Drug-Related Treatment-Emergent AE	343 (45.8%)	250 (66.7%)	203 (57.2%)
Subjects Experiencing Any Grade 3 or 4 Study-Drug-Related Treatment-Emergent AE	20 (2.7%)	15 (4.0%)	13 (3.7%)
Subjects Experiencing Any Treatment-Emergent SAE	69 (9.2%)	25 (6.7%)	31 (8.7%)
Subjects Experiencing Any Study-Drug-Related Treatment-Emergent SAE	5 (0.7%)	7 (1.9%)	2 (0.6%)
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	26 (3.5%)	19 (5.1%)	18 (5.1%)
Subjects who had Treatment-Emergent Death[a]	1 (0.1%)	2 (0.5%)	3 (0.8%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; SAE, serious adverse event; TVD, Truvada

a Treatment-emergent death refers to deaths occurring between the first dose date and the last dose date plus 30 days (inclusive).

Table 20. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Treatment-Emergent Adverse Events Reported for at Least 5% of Subjects in Any Treatment Group (Pooled Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a, b, c]	QUAD 236-0104, 0102, 0103 (N = 749)	ATR 236-0104, 0102 (N = 375)	ATV/r+TVD 236-0103 (N = 355)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	694 (92.7%)	355 (94.7%)	333 (93.8%)
Eye Disorders	41 (5.5%)	25 (6.7%)	78 (22.0%)
Ocular Icterus	2 (0.3%)	0	51 (14.4%)
Gastrointestinal Disorders	403 (53.8%)	168 (44.8%)	201 (56.6%)
Diarrhea	170 (22.7%)	70 (18.7%)	97 (27.3%)
Nausea	146 (19.5%)	50 (13.3%)	69 (19.4%)
Vomiting	41 (5.5%)	16 (4.3%)	24 (6.8%)
Flatulence	28 (3.7%)	5 (1.3%)	29 (8.2%)
General Disorders and Administration Site Conditions	176 (23.5%)	106 (28.3%)	94 (26.5%)
Fatigue	98 (13.1%)	49 (13.1%)	45 (12.7%)
Pyrexia	26 (3.5%)	19 (5.1%)	14 (3.9%)
Hepatobiliary Disorders	8 (1.1%)	7 (1.9%)	38 (10.7%)
Jaundice	0	1 (0.3%)	31 (8.7%)
Infections and Infestations	470 (62.8%)	224 (59.7%)	232 (65.4%)
Upper Respiratory Tract Infection	106 (14.2%)	44 (11.7%)	58 (16.3%)
Nasopharyngitis	53 (7.1%)	21 (5.6%)	28 (7.9%)
Sinusitis	41 (5.5%)	33 (8.8%)	18 (5.1%)
Bronchitis	49 (6.5%)	22 (5.9%)	18 (5.1%)
Musculoskeletal and Connective Tissue Disorders	160 (21.4%)	61 (16.3%)	55 (15.5%)
Back Pain	42 (5.6%)	14 (3.7%)	13 (3.7%)
Nervous System Disorders	201 (26.8%)	154 (41.1%)	93 (26.2%)
Headache	109 (14.6%)	38 (10.1%)	44 (12.4%)
Dizziness	42 (5.6%)	89 (23.7%)	25 (7.0%)
Somnolence	11 (1.5%)	29 (7.7%)	4 (1.1%)
Psychiatric Disorders	209 (27.9%)	174 (46.4%)	81 (22.8%)
Abnormal Dreams	70 (9.3%)	103 (27.5%)	14 (3.9%)
Insomnia	65 (8.7%)	51 (13.6%)	18 (5.1%)

Adverse Events by System Organ Class and Preferred Term[a, b, c]	QUAD 236-0104, 0102, 0103 (N = 749)	ATR 236-0104, 0102 (N = 375)	ATV/r+TVD 236-0103 (N = 355)
Depression	57 (7.6%)	41 (10.9%)	23 (6.5%)
Respiratory, Thoracic and Mediastinal Disorders	151 (20.2%)	89 (23.7%)	76 (21.4%)
Cough	42 (5.6%)	17 (4.5%)	28 (7.9%)
Oropharyngeal Pain	29 (3.9%)	27 (7.2%)	18 (5.1%)
Skin and Subcutaneous Tissue Disorders	200 (26.7%)	137 (36.5%)	102 (28.7%)
Rash	52 (6.9%)	47 (12.5%)	22 (6.2%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; MedDRA, Medical Dictionary for Regulatory Authorities; SAE, serious adverse event; SOC, system organ class; TVD, Truvada

a AEs were coded using MedDRA 14.0.

b SOC was presented alphabetically, and PT was presented by decreasing order based on the total frequencies.

c Multiple AEs were counted only once per subject for each SOC and PT.

8.6.2. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

Deaths

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, the overall incidence of deaths, SAEs, and discontinuation due to AEs was low. Six treatment-emergent deaths were reported (QUAD 0.1%, 1 subject; Atripla 0.5%, 2 subjects; ATV/r+TVD 0.8%, 3 subjects). A suicide death (Atripla group) was considered related to study drug by the investigator; no other fatal event was considered related to study drug by the investigator.

SAEs

Similar percentages of subjects in the QUAD, Atripla, and ATV/r+TVD groups reported any SAE (QUAD 9.2%, 69 subjects; Atripla 6.7%, 25 subjects; ATV/r+TVD 8.7%, 31 subjects). No individual SAE was reported in more than 1% of subjects in any treatment group. The difference observed between the QUAD and Atripla groups was driven predominantly by SAEs in the Infections and Infestations system organ class (SOC), all of which were considered by the investigator to be unrelated to study drug. The overall (ie, serious and nonserious) Infections and Infestations AEs percentages were balanced between all 3 treatment groups (QUAD 62.8%, 470 subjects; Atripla 59.7%, 224 subjects; ATV/r+TVD 65.4%, 232 subjects); thus there was no evidence of increased infection AEs overall in the QUAD group.

The overall incidence of SAEs considered related to study drug by the investigator was also low. A lower percentage of subjects in the QUAD group compared with the Atripla group experienced SAEs considered related to study drug by the investigator (QUAD 0.7%, 5 subjects; Atripla 1.9%, 7 subjects. Similar percentages of subjects in the QUAD and ATV/r+TVD groups reported any SAE considered related to study drug by the investigator (ATV/r+TVD 0.6%, 2 subjects). No individual SAE considered related to study drug by the investigator was reported for more than 1 subject in any treatment group. The difference observed between the QUAD and Atripla groups was driven predominantly by study-drug-related SAEs reported in the Nervous System Symptoms and Psychiatric Disorders SOCs, consistent with the Atripla prescribing information.

Discontinuations due to AEs

A lower percentage of subjects in the QUAD group compared with the Atripla and ATV/r+TVD groups discontinued due to an AE (QUAD 3.5%, 26 subjects; Atripla 5.1%, 19 subjects; ATV/r+TVD 5.1%, 18 subjects). No individual AE that resulted in study drug discontinuation was reported in more than 1% of subjects in the QUAD or Atripla treatment groups. In the ATV/r+TVD group, AEs that resulted in study drug discontinuation reported in more than 1% of subjects (1.1%, 4 subjects in each case) were ocular icterus (vs 0 subjects in the QUAD group) and nausea (vs 0.3%, 2 subjects in the QUAD group). The difference observed between the QUAD and Atripla groups was driven predominantly by discontinuations in the Atripla group due to AEs in the Psychiatric Disorders and Skin and Subcutaneous Tissue Disorders SOCs. These results are consistent with the Atripla prescribing information. The difference observed between the QUAD and ATV/r+TVD groups was driven predominantly by discontinuations in the ATV/r+TVD group due to AEs in the Eye Disorders and Hepatobiliary Disorders SOCs. These results are consistent with the ATV prescribing information.

QUAD Safety Update Data Cut

In the QUAD safety update data cut (21 November 2011) for the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, the overall incidence of SAEs was low. The frequency of SAEs in the QUAD treatment group was 9.2% (69 subjects) in the QUAD pooled safety data for the original NDA and 10.5% (80 subjects) in the double-blind and open-label phases in the safety update. Each new SAE was reported in only 1 additional subject except for cellulitis, which was reported in 2 additional subjects; none of the new SAEs were considered related to study drug by the investigator. There were no new deaths in any of the treatment groups. Four additional subjects since the original NDA had AEs that led to discontinuation of QUAD due to hepatosplenomegaly and hepatic steatosis, intentional overdose and suicidal behavior, Burkitt's lymphoma, and blood creatinine increased.

8.6.3. Clinical Laboratory Abnormalities

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, the majority of subjects had at least 1 treatment-emergent laboratory

abnormality reported. The majority of the abnormalities reported were Grade 1 or 2 in severity. Treatment-emergent Grade 3 or 4 abnormalities were reported less frequently in the QUAD group than in the Atripla group or the ATV/r+TVD group (QUAD 12.1% of subjects with maximum Grade 3 and 3.9% of subjects with maximum Grade 4 abnormalities; Atripla 14.0% of subjects with maximum Grade 3 and 9.7% of subjects with maximum Grade 4 abnormalities; ATV/r+TVD 52.0% of subjects with maximum Grade 3 and 15.9% of subjects with maximum Grade 4 abnormalities).

The most frequently reported Grade 3 or 4 abnormalities were as follows:

- QUAD group — lipase (8.1% Grade 3, 3.2% Grade 4, n = 62), creatine kinase (3.5% Grade 3, 1.7% Grade 4, n = 745), and hematuria (2.8% Grade 3, n = 745)

- Atripla group — lipase (13.9% Grade 3, 2.8% Grade 4, n = 36), creatine kinase (4.0% Grade 3, 6.7% Grade 4, n = 372), and GGT (3.5% Grade 3, 1.3% Grade 4, n = 372)

- ATV/r+TVD group — total bilirubin (48.0% Grade 3, 10.2% Grade 4, n = 352), lipase (18.2% Grade 3, 3.0% Grade 4, n = 33), and creatine kinase (2.8% Grade 3, 4.5% Grade 4, n = 352)

As shown in the frequencies described above, Grade 3 or 4 creatine kinase was reported less frequently in the QUAD group than in the Atripla group, and Grade 3 or 4 lipase and total bilirubin were reported less frequently in the QUAD group than in the ATV/r+TVD group.

8.7. Renal Safety Profile

Assessments of renal safety included the following: a summary of renal events, renal events that led to study drug discontinuation, and a description of other subjects with abnormal selected renal laboratory parameters in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103. In addition, renal laboratory parameters were systematically assessed. Since renal events were identified as events of interest for regimens. To further characterize the renal safety profile of COBI when used in combination with TDF, a review of renal events leading to study drug discontinuation was also conducted with the Phase 2 and 3 studies (GS-US-216-0105 and GS-US-216-0114) with COBI.

8.7.1. Renal Adverse Events, Renal Adverse Events Leading to Study Drug Discontinuation, and Renal Laboratory Abnormalities for Individual Subjects

In the pooled analyses of Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, 12 subjects (1.6%) in the QUAD group had renal AEs (4 renal failure, 1 acquired Fanconi syndrome, 7 increased blood creatinine), 2 subjects (0.5%) in the Atripla group had renal AEs (renal failure and increased blood creatinine), and 2 subjects (0.6%) in the ATV/r+TVD group had renal AEs (increased blood creatinine and toxic nephropathy). Seven subjects discontinued study drug due to renal AEs, 6 in the QUAD group and 1 in the ATV/r+TVD group. The subject in the ATV/r+TVD group discontinued due to an AE of

toxic nephropathy with elevated creatinine and tubular involvement, which improved after discontinuation of study drug. Of the 6 subjects who discontinued QUAD therapy due to renal AEs, none were reported as SAEs. Five subjects out of the 6 had evidence of renal impairment at baseline (eGFR < 90 mL/min or proteinuria ≥ +1).

Of the 6 subjects who discontinued QUAD therapy in the QUAD group:

- 2 subjects had small increases (~0.2 to 0.3 mg/dL) in serum creatinine without tubular dysfunction within weeks of initiation the QUAD STR. For 1 subject, serum creatinine levels returned to baseline after study drug discontinuation, reflecting the effect of COBI on serum creatinine. For the other subject, serum creatinine levels improved but did not return to baseline due to the subject switching to an RTV-boosted PI regimen.

- 2 subjects had rapid increases in serum creatinine with tubular dysfunction within a few weeks of initiation the QUAD STR. For both subjects, renal abnormalities improved or resolved soon after discontinuation of the QUAD STR. Both subjects had either screening or baseline eGFR < 70 mL/min and violated the study protocol because the subjects were not discontinued from QUAD when their eGFR decreased below 50 mL/min (per protocol-defined stopping rules based on prescribing information for FTC and TDF).

- 2 subjects showed slow and gradual increases in serum creatinine with tubular dysfunction over months after initiation with the QUAD STR, which improved after discontinuation of study drug.

Glomerular and tubular renal laboratory parameters improved or resolved after study drug discontinuation for all subjects who discontinued QUAD due to renal AEs. Details from these cases are provided in Appendix 5.

In summary, renal events leading to study drug discontinuation in the QUAD group were infrequent (< 1%, 6 of 749 subjects), and 5 of the 6 events occurred in subjects with baseline renal impairment. The observed renal events were identifiable through routine laboratory monitoring. The type of events and the rate at which they were reported are consistent with TDF postmarketing surveillance and published literature {15873}, {14062}, {12302}, {14592}, {14110}, {14108}, {18498}, {9341}, {12249}, {19273}, {18038}, {19105}, {10921}, {7013}, {10961}, {13023}, {19102}, {11299} (Section 8.17).

In the QUAD safety update data cut (21 November 2011) for Studies GS-US-236-0102, GS-US-236-0103, an additional subject (b) (6)) discontinued QUAD therapy due to an AE of increased blood creatinine. After discontinuation of QUAD, the subject's laboratory values returned to baseline values (Appendix 5).

In the randomized phase of Studies GS-US-216-0105 and GS-US-216-0114 (QUAD safety update data cut), 6 subjects in the ATV/co+TVD group and 6 subjects in the ATV/r+TVD group discontinued due to renal AEs. Eleven of the 12 events that led to discontinuation during the randomized phase occurred in Study GS-US-216-0114. One subject from Study

GS-US-216-0105 (b) (6)), who was initially randomized to ATV/r+TVD, discontinued open-label ATV/co+TVD due to a renal AE during the open-label phase; this subject also had a renal AE during the randomized phase that did not lead to discontinuation of ATV/r+TVD. These discontinuations occurred either in the period evaluated for the primary safety analysis set or with additional follow up in the All ATV/co+TVD dose group (ie, all subjects who received at least 1 dose of ATV/co+TVD). Of the 6 subjects who discontinued ATV/co+TVD during the randomized phase due to renal AEs, 2 subjects (b) (6) and (b) (6)) reported a renal SAE. Of the 6 subjects who discontinued ATV/r+TVD during the randomized phase, 3 subjects ((b) (6)) reported a renal SAE. Renal laboratory abnormalities improved in all subjects, and were reverted to baseline upon discontinuation of ATV/co+TVD in most subjects. Details from these cases are provided in Appendix 6.

In summary, renal events leading to study drug discontinuation in the COBI group were infrequent (1.5%, 6 of 394 subjects) and were identifiable through routine laboratory monitoring. The type of events and the rate at which they were reported are consistent with TDF postmarketing surveillance and published literature.

8.7.1.1. Analyses of Renal Laboratory Abnormalities for Possible Glomerular and Tubular Involvement

To identify other potential subclinical renal cases that may not have been reported as AEs by the investigator, comprehensive analyses of renal laboratory abnormalities for possible glomerular involvement (confirmed serum creatinine increase ≥ 0.4 mg/dL) and tubular involvement (confirmed 1-grade shift in hypophosphatemia, or confirmed 2-grade shift in glycosuria or proteinuria) were performed using the QUAD NDA integrated summary of safety (ISS) data cut and confirmed in the safety update data cut.

An increase ≥ 0.4 mg/dL (= mean change + 2×SD = 0.14 + [2 × 0.13]) was chosen as a conservative threshold to define potential glomerular involvement due to the following considerations:

- Administration of COBI can lead to elevation in serum creatinine due to its inhibitory effect on renal tubular creatinine secretion.

- The mean change from baseline at Week 48 in serum creatinine was 0.14 mg/dL (SD = 0.13 mg/dL) among subjects in the QUAD group. Therefore, an increase of 0.4 mg/dL was chosen (= mean change + 2×SD = 0.14 + [2 × 0.13]). Mean changes from baseline that were ≥ 0.4 mg/dL represent changes beyond the effect caused by COBI blocking creatinine secretion. The mean value of serum creatinine at baseline is ~1.0 mg/dL in QUAD studies.

- The lower cutoff for Grade 1 serum creatinine elevation is > 1.5 mg/dL.

Of the 749 subjects in the QUAD group (Integrated Summary of Safety [ISS] NDA data cut), 18 subjects (2.4%) had confirmed increase of serum creatinine ≥ 0.4 mg/dL; of these,

14 subjects (1.9%) had no other laboratory signs of renal changes. The other 4 subjects (0.5%) were previously discussed in Section 8.7.1 (ie, subjects who discontinued study drug with tubular involvement: Subjects (b) (6)). Subjects who discontinued the QUAD STR due to renal AEs are tabulated in Appendix 5.

Of the 749 subjects in the QUAD group (ISS NDA data cut), 731 subjects (97.6%) did not have confirmed serum creatinine increase ≥ 0.4 mg/dL. Of these, 721 (96.3%) had no other treatment-emergent laboratory signs of renal changes, although 2 subjects ((b) (6) and (b) (6) , Appendix 5) had renal AEs that led to discontinuation of study drug. Ten subjects (1.3%) did not have confirmed serum creatinine increase ≥ 0.4 mg/dL, but had another renal laboratory abnormality: 6 subjects had glycosuria, 3 had hypophosphatemia, and 1 had proteinuria. All of the 6 subjects with glycosuria had at least Grade 1 hyperglycemia or history of diabetes, all 3 subjects with hypophosphatemia improved while continuing study drug, and 1 subject with proteinuria had trace proteinuria at screening and baseline. None of these 10 subjects had reported renal AEs and all continued on QUAD.

When the same analyses were performed with the QUAD safety update data cut, 4 additional subjects in the QUAD group had confirmed increase of serum creatinine ≥ 0.4 mg/dL. None of these subjects discontinued QUAD or had reported renal AEs. One of the 4 subjects ((b) (6)) had hypophosphatemia.

8.7.2. Renal Laboratory Parameters

8.7.2.1. Serum Creatinine and Estimated GFR

Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

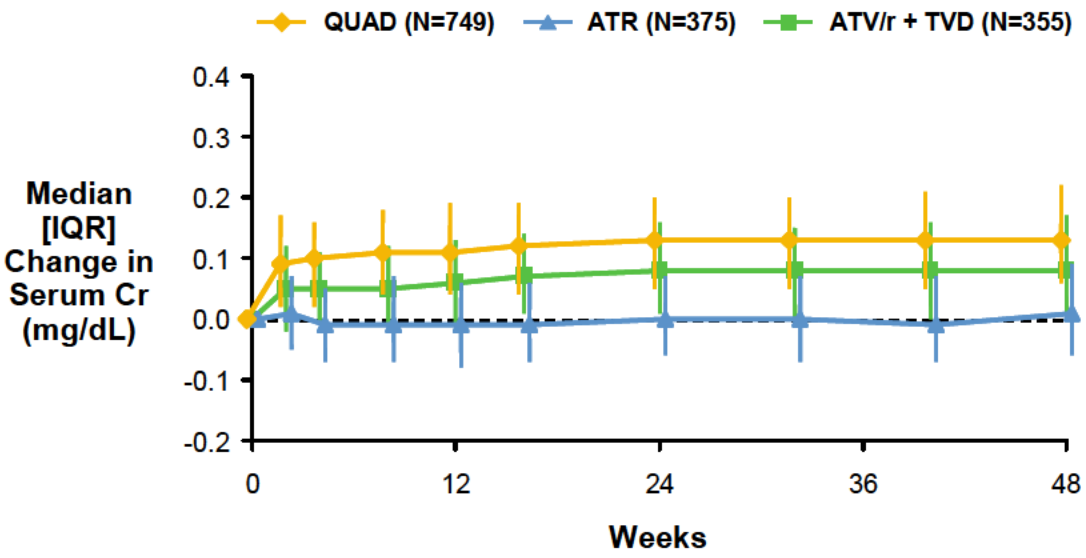
In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, increases in median values for serum creatinine in the QUAD group were noted as early as Week 2 (median change from baseline at Week 2 was 0.09 mg/dL), after which they generally stabilized through Week 48 (median change from baseline at Week 48 was 0.13 mg/dL). The pattern of change in serum creatinine in the ATV/r+TVD group was similar; however, the changes were smaller than those seen in the QUAD group (median change from baseline at Week 2 was 0.05 mg/dL; median change from baseline at Week 48 was 0.08 mg/dL). There were no notable changes from baseline in median values for serum creatinine in the Atripla group.

Consistent with the findings for serum creatinine, a small decrease in median $eGFR_{CG}$ was observed in the QUAD group (baseline median 114.2 mL/min; the median change from baseline at Week 48 was –13.5 mL/min; Figure 9). Decreases in $eGFR_{CG}$ were seen as early as Week 2, with only minimal additional decreases after that time point; median values remained within the normal range. There were small decreases from baseline in median values for $eGFR_{CG}$ in the ATV/r+TVD group (baseline median 114.7 mL/min; the median change from baseline at Week 48 was –9.5 mL/min). There were small decreases from baseline in median values for $eGFR_{CG}$ in the Atripla group; however, these were seen inconsistently across study visits. Results for cystatin C-derived GFR (cysGFR; cystatin C is

an endogenous probe almost exclusively filtered with no secretion or reabsorption) showed small increases in all treatment groups.

No relevant exposure changes in creatinine or $eGFR_{CG}$ trends were observed in PK/PD analyses. Across all EVG, COBI, FTC, or TFV AUC_{tau} quartiles, the maximum increase from baseline in serum creatinine and maximum decrease in $eGFR_{CG}$ were comparable.

Figure 9. **GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Median (Q1, Q3) of Change from Baseline in Serum Creatinine (Pooled Safety Analysis Set)**



ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; $eGFR_{CG}$; IQR, interquartile range; TVD, Truvada

The findings in the Phase 2 and 3 QUAD studies are consistent with those in COBI Study GS-US-216-0121, which showed that COBI produces a small increase in serum creatinine that results in a small decrease in eGFR, but COBI does not affect aGFR when measured with a probe drug (iohexol). The data for cysGFR in Studies GS-US-236-0104, GS-US-236-0102, GS-US-236-0103, and for aGFR in Study GS-US-216-0121, confirm that COBI does not affect actual renal glomerular function. The findings are consistent with the inhibition of tubular secretion of creatinine by COBI. In addition, the magnitude of the changes in serum creatinine and $eGFR_{CG}$ was similar in subjects who received COBI or RTV in Studies GS-US-236-0104, GS-US-236-0102, GS-US-236-0103, or GS-US-216-0105, demonstrating a small but consistent effect on serum creatinine and $eGFR_{CG}$ with both pharmacoenhancers.

Serum Phosphorus and Urine Fractional Excretion of Phosphate

Median values for serum phosphorus were within normal ranges throughout Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103. Hypophosphatemia occurred infrequently overall, and Grade 3 hypophosphatemia was reported for only 1 subject who received QUAD (at a single study visit) in Study GS-US-236-0102 and for 2 subjects who received ATV/r+TVD in Study GS-US-236-0103. Urine fractional excretion of phosphate increased similarly and slightly in both treatment groups in Study GS-US-236-0102 and in both treatment groups in Study GS-US-236-0103.

Glycosuria

Glycosuria was not reported in Study GS-US-236-0104 and was reported infrequently in Studies GS-US-236-0102 and GS-US-236-0103. In the pooled safety analysis set, treatment-emergent Grade 3 glycosuria was reported for 13 subjects (QUAD 0.8%, 6 subjects; Atripla 0.5%, 2 subjects; ATV/r+TVD 1.4%, 5 subjects), most of whom had graded hyperglycemia and notable urine glucose at screening or baseline.

Proteinuria

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, treatment-emergent graded proteinuria was observed for a higher percentage of subjects in the QUAD group compared with the Atripla or ATV/r+TVD groups (QUAD 38.1%, 284 subjects; Atripla 28.8%, 107 subjects; ATV/r+TVD 24.1%, 85 subjects). Proteinuria was predominantly Grade 1 in severity. Grade 3 proteinuria was reported for 0.3% of subjects in the QUAD and ATV/r+TVD groups (QUAD 2 subjects, ATV/r+TVD 1 subject). For all 3 subjects, Grade 3 proteinuria was observed at a single study visit and resolved/reduced at the next study visit with no action taken with study drug.

To further investigate the observed differences between groups in the incidence of low-grade proteinuria, additional exploratory analyses were performed to assess baseline and postbaseline urine protein relative to actual values reported (negative, trace, +1, +2, +3, +4). Among subjects with no protein in the urine at baseline (ie, negative result at baseline), similar percentages of subjects in each treatment group had confirmed proteinuria (trace or worse) during study treatment (QUAD 38.6%, 186 subjects; Atripla 42.9%, 109 subjects; ATV/r+TVD 36.3%, 85 subjects); for most of these subjects, this was confirmed trace proteinuria (QUAD 34.0%, 164 subjects; Atripla 40.2%, 102 subjects; ATV/r+TVD 32.1%, 75 subjects).

8.7.3. Renal Postmarketing Data

Surveillance of postmarketing spontaneous AE reports has provided evidence that TDF therapy may cause renal adverse reactions. These reactions include renal failure (including acute renal failure), Fanconi syndrome, and proximal renal tubulopathy. The spontaneous reporting rates for these events are provided in Table 21 and are based on an estimated 5 million patient-years of postmarketing exposure to TDF-containing Gilead marketed products.

Table 21. Spontaneous Reporting Rates for Selected Renal Adverse Events

Adverse Event (MedDRA Preferred Term)	Reporting Rate (per 10,000 patient-years)
Renal failure (including renal failure acute)	1.6
Fanconi syndrome acquired	0.7
Renal tubular disorder	0.3

MedDRA, Medical Dictionary for Regulatory Authorities

Other renal adverse reactions include acute tubular necrosis, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, and polyuria.

TDF-associated renal toxicity is thought to be mainly due to an effect on proximal renal tubules. Although the molecular mechanism is not fully understood, it is plausible that renal toxicity might be a consequence of disrupted transport equilibrium between the tubular uptake and efflux of TFV due to genetic polymorphism in renal transporters.

The following adverse reactions may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia (manifested as bone pain and infrequently contributing to fractures), hypokalemia, muscular weakness, myopathy, and hypophosphatemia. These events are not considered to be causally associated with TDF therapy in the absence of proximal renal tubulopathy.

8.8. Bone Safety Profile

Bone toxicity, including a reduction in BMD, was seen in animals following treatment with TFV or tenofovir disoproxil. Reduction in BMD of 2% to 4% has been seen in most clinical studies starting therapy in HIV-1 antiretroviral treatment-naive subjects, including those starting on TDF. Those reductions occur in the first 24 to 48 weeks and then stabilize {14193}. In Study 903E, a reduction in BMD of 3.4% in spine and 3.3% in hip were found at Week 48, but had no progression out to 10 years of follow-up, with total BMD reduction at year 10 found to be 2.5% for spine and 2.9% for hip {20128}. Clinically relevant bone abnormalities have not been seen in long-term (> 3 years) clinical studies in HIV-1 infected adults treated with TDF. However, postmarketing safety data indicate that bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected, appropriate consultation should be obtained.

EVG, COBI, and FTC are not considered to have effects on bone safety.

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, prespecified fracture events included all PTs with “fracture” as the primary or secondary Medical Dictionary for Regulatory Activities (MedDRA) high level group term. Bone fractures were reported for similar percentages of subjects in each

treatment group (QUAD 1.3%, 10 subjects; Atripla 1.6%, 6 subjects; ATV/r+TVD 1.7%, 6 subjects; p = 0.79 for comparison of QUAD vs Atripla, and p = 0.60 for comparison of QUAD vs ATV/r+TVD). One fracture for a subject in the QUAD group was reported in Study GS-US-236-0104; all other fractures were reported in Studies GS-US-236-0102 and GS-US-236-0103. The majority of the reported fractures occurred due to traumatic injury.

In a subset of subjects at selected sites in Study GS-US-236-0103 for whom dual-energy x-ray absorptiometry (DEXA) scans were performed, there were smaller mean percentage decreases from baseline in BMD at the lumbar spine and hip in the QUAD group compared with the ATV/r+TVD group (changes at Week 48: spine –2.63% in the QUAD group vs –3.33% in the ATV/r+TVD group; hip –3.06% in the QUAD group vs –3.88% in the ATV/r+TVD group); however, the differences between groups were not statistically significant.

8.9. Neurological and Psychiatric Events

Certain neurological and psychiatric events are associated with NNRTIs, especially EFV {20239}; these events were therefore considered important AEs for comparison between the QUAD and Atripla STRs. Neurological and psychiatric effects are not considered to be important safety concerns for EVG, COBI, FTC, or TDF; however, dizziness has been identified as an adverse drug reaction (ADR) to FTC and TDF in clinical studies, and headache, insomnia, and abnormal dreams have been identified as ADRs to FTC in clinical studies.

In the pooled safety analysis set in Studies GS-US-236-0104 and GS-US-236-0102, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported any important neurological or psychiatric AEs based on a prespecified analysis (QUAD 42.9%, 170 subjects; Atripla 62.1%, 233 subjects; p < 0.001). Results for the Atripla group are consistent with the Atripla prescribing information.

The most frequently reported important neurological and psychiatric AEs were as follows:

- QUAD group — abnormal dreams (14.6%, 58 subjects), headache (14.1%, 56 subjects), and depression (9.3%, 37 subjects)

- Atripla group — abnormal dreams (27.5%, 103 subjects), dizziness (23.7%, 89 subjects), and insomnia (13.6%, 51 subjects)

Neurological and psychiatric AE PTs generally were reported for a lower percentage of subjects in the QUAD group than in the Atripla group, with the one notable exception of headache (QUAD 14.1%, 56 subjects; Atripla 10.1%, 38 subjects).

Serious neurological and psychological AEs were reported for 5 subjects (1.3%) in each treatment group. Serious neurological and psychological AEs reported for more than 1 subject were headache (QUAD 2 subjects; Atripla 1 subject); suicide attempt (Atripla 2 subjects); completed suicide (1 subject per group); and depression (1 subject per group). Neurological and psychiatric AEs led to study drug discontinuation for 4 subjects

(1.0%) in the QUAD group and for 8 subjects (2.1%) in the Atripla group. In Study GS-US-236-0102, 2 AEs (1 per treatment group) of completed suicide were fatal; the suicide death in the Atripla group was considered related to study drug by the investigator.

8.10. Rash Events

Rash events are associated with NNRTIs and with PIs {20239}; therefore, these events were considered important AEs for comparison between the QUAD STR and comparator regimens investigated in Phase 2 and 3 studies. Rash events are not considered to be an important safety concern for EVG, COBI, FTC, or TDF; however, rash events and mild skin hyperpigmentation have been reported in HIV-1 patients treated with FTC, and rash has been identified as an ADR to TDF in postmarketing experience.

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported any rash AE based on a prespecified analysis (QUAD 17.5%, 131 subjects; Atripla 27.7%, 104 subjects; $p < 0.001$). No statistically significant difference in the incidence of rash AEs was seen between the QUAD and ATV/r+TVD groups (ATV/r+TVD 18.0%, 64 subjects; $p = 0.87$). The most frequently reported important rash AEs were as follows:

- QUAD group — rash (6.9%, 52 subjects), dermatitis (2.7%, 20 subjects), and pruritis (2.0%, 15 subjects)
- Atripla group — rash (12.5%, 47 subjects), dermatitis (3.5%, 13 subjects), and pruritis (3.5%, 13 subjects)
- ATV/r+TVD group — rash (6.2%, 22 subjects), dermatitis (2.5%, 9 subjects), and eczema (2.0%, 7 subjects)

Thus, even among the most frequently reported rash AE PTs in the QUAD group, the percentages of subjects with these events in the QUAD group was lower than in the Atripla group.

No rash SAEs were reported in the QUAD group; rash SAEs were reported for 1 subject (0.3%) in each of the Atripla and ATV/r+TVD groups. Rash AEs led to study drug discontinuation for 1 subject (0.1%) in the QUAD group and 4 subjects (1.1%) in each of the Atripla and ATV/r+TVD groups.

8.11. Liver-Related Laboratory Tests

Hepatotoxicity has been reported for most antiretroviral therapies {20239}. For the EFV component of Atripla, hepatic enzyme increases have been reported, and hepatic failure including progression to transplantation or death have been reported in a few postmarketing cases {17599}. Most patients receiving ATV experience asymptomatic elevations in bilirubin {17624}.

EVG and COBI are not considered to have any effect on liver parameters. Hepatic effects are not considered to be an important safety concern for FTC and TDF other than risks of posttreatment hepatic flares in HIV/HBV coinfected patients; however, increased AST and/or increased ALT and hyperbilirubinemia are included as ADRs for FTC, and hepatic steatosis, hepatitis, and increased liver enzymes (most commonly AST, ALT, and GGT) are included as an ADR for TDF.

Lower percentages of subjects in the QUAD group than in the Atripla group had graded elevations of ALT, AST, GGT, and alkaline phosphatase (Grade 4 ALT occurred in 0.8% of subjects in both treatment groups).

Lower percentages of subjects in the QUAD group than in the ATV/r+TVD group had graded abnormalities of ALT and AST reported. Graded abnormalities in GGT and alkaline phosphatase were reported for a similar percentage of subjects in both treatment groups. Graded total bilirubin elevations were reported for a lower percentage of subjects in the QUAD group than in the ATV/r+TVD group.

Based on a prespecified summary of liver-related laboratory test results relative to the ULN, total bilirubin elevations to > 2 times the ULN were reported infrequently in the QUAD group (0.9%, 7 subjects) and in the Atripla group (0.3%, 1 subject); however, such elevations were reported frequently in the ATV/r+TVD group (74.7%, 263 subjects). Direct bilirubin elevations above the ULN were reported infrequently in the QUAD and Atripla groups (QUAD 0.9%, 7 subjects; Atripla 0.5%, 2 subjects); however, such elevations were reported frequently in the ATV/r+TVD group (22.2%, 78 subjects). Elevations of AST or ALT to > 3 times the ULN along with elevations in total bilirubin to > 2 times the ULN were reported for a lower percentage of subjects in the QUAD group than in the ATV/r+TVD group (QUAD 0.3%, 2 subjects; ATV/r+TVD 4.0%, 14 subjects [Atripla 0 subjects]). Of the 2 subjects in the QUAD group, 1 had a history of alcohol abuse, and 1 had HCV infection reported during the study. Elevations of transaminases and total bilirubin in the ATV/r+TVD group are consistent with the ATV prescribing information.

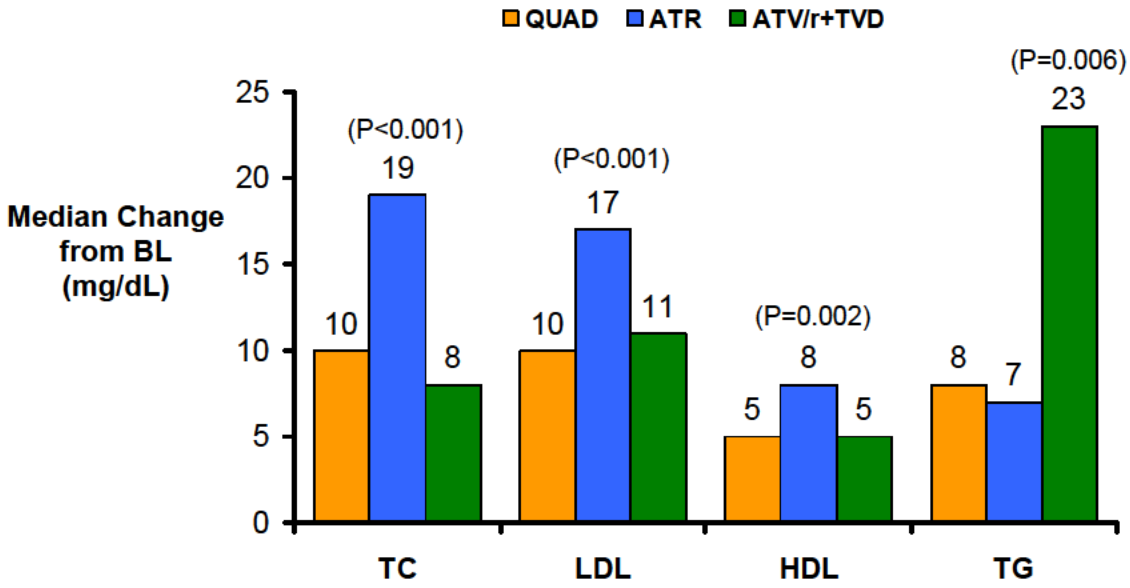
8.12. Fasting Glucose and Lipid Parameters

Dyslipidemia is an important cardiovascular risk factor and is frequently reported in HIV-1 infected patients. It has been associated with NNRTIs, PIs, and NRTIs {20239}. EFV and ATV/r have been associated with increases in triglycerides, LDL cholesterol, and HDL cholesterol. Treatment guidelines identify stavudine, zidovudine (ZDV), and abacavir as more strongly associated with dyslipidemia than other NRTIs such as FTC and TDF.

In the pooled safety analysis set in Studies GS-US-236-0102 and GS-US-236-0103, mean increases from baseline through Week 48 in fasting total cholesterol, LDL cholesterol, and HDL cholesterol were significantly lower for the QUAD group compared with the Atripla group (Figure 10). Mean increases from baseline through Week 48 in fasting triglycerides were lower for the QUAD group compared with the ATV/r+TVD group. In all treatment groups, there were increases from baseline in mean values for fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; however, mean values remained in the

normal range for each analyte. Abnormalities in fasting glucose and lipid parameters were generally Grade 1 or 2 in severity. No pattern in the occurrence of Grade 3 or 4 abnormalities was apparent.

Figure 10. GS-US-236-0102 and GS-US-236-0103: Change in Fasting Lipids at Week 48 (Pooled Safety Analysis Set)



ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; BL, baseline; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

Note: All comparisons are with the QUAD STR.

8.13. Thyroid Stimulating Hormone, T3, and T4

Potential toxicities related to COBI observed in nonclinical toxicology studies included adaptive thyroid changes. The thyroid effects are considered rodent specific, and predispose rats, but not humans, to thyroid neoplasms. Changes in TSH, T3, and T4 were assessed in Study GS-US-236-0104. No clinically relevant changes from baseline in median values for TSH, T3, or T4 were observed in either group during the randomized phase of this study.

8.14. Immunoglobulins

Potential toxicities related to COBI observed in nonclinical toxicology studies included lower IgG antibody titers in a single study in female rats. Changes in IgG and IgM were assessed in Study GS-US-236-0104. In this study, there were small decreases in median values for IgG and IgM in both groups; however median values remained in the normal range. The observed changes were not associated with infection, malignancy, or conditions related to immunodeficiency, and overall, the nonclinical findings are not considered to be relevant in the clinical setting.

In the pooled analysis set for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, comparable rates of infections were seen between male and female subjects (62.4% [421 of 675] of males and 66.2% [49 of 69] of females experienced an AE in the Infections and Infestations SOC).

8.15. Electrocardiogram and Echocardiogram Findings

COBI showed the potential to prolong the PR interval and decrease LV function in isolated rabbit hearts, and a tendency to slightly prolong the PR interval in dogs. These effects may be a consequence of interaction with cardiac calcium channels {11876}, {11873}.

In Study GS-US-216-0107, an expected, modest dosing-related increase in PR interval (~4 to 5 msec at exposures corresponding to multiple COBI 150-mg dose exposures observed with QUAD STR) between 3 and 5 hours after dosing was observed that was not considered to be clinically significant (Section 5.1.3.2.2). No clinically significant AEs, ECG abnormalities, or changes in physical exams or vital signs were observed. Study GS-US-216-0116, at COBI 150-mg dose and corresponding exposures, demonstrated no clinically relevant changes in the LV function, with all 3 measures (end-systolic volume, end-diastolic volume, and ejection fraction) in the normal range based on time-matched ECHO assessments.

In Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, clinically significant (as assessed by the investigator) ECG abnormalities were reported for were reported for 4 subjects who received the QUAD STR (atrial fibrillation [2 subjects], sinus bradycardia, and LV hypertrophy with repolarization abnormality), 2 subjects who received Atripla (ST and T wave abnormality [considered inferolateral ischemia] and sinus bradycardia). The 4 subjects in the QUAD group continued on study drug. Three of the 4 ECG abnormalities in the QUAD group were reported as AEs at the time of the ECG findings (LV hypertrophy along with cardiac murmur and ECG repolarization abnormality, atrial fibrillation, and sinus bradycardia).

8.16. Safety in Special Populations

Adverse events from Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 were summarized by demographic characteristics (age, sex, and race) and by baseline disease characteristics (HIV-1 RNA level and CD4 cell count).

Pertinent data for the individual components of QUAD are also summarized in this section to support proposed prescribing information for patients with renal impairment, hepatic impairment, those coinfected with HIV-1 and HBV or HCV, and for patients who are pregnant or lactating.

8.16.1. Age

No PK studies have been conducted with the QUAD STR in subjects under the age of 18 years. The safety and efficacy of the QUAD STR have not been established in patients under the age of 18 years. The QUAD STR should not be administered to patients under the age of 18 years.

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, similar percentages of subjects < 40 or ≥ 40 years of age in each group reported any AE (Table 22). Overall, no differences between age groups were apparent in the pattern of AEs reported.

Table 22. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Number of Treatment-Emergent Adverse Events by Age Group (< 40 Years or ≥ 40 Years) (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103		ATR 236-0104, 0102		ATV/r+TVD 236-0103	
N (%)	< 40 (N = 437)	≥ 40 (N = 312)	< 40 (N = 213)	≥ 40 (N = 162)	< 40 (N = 193)	≥ 40 (N = 162)
Number of Subjects Experiencing any Treatment-Emergent AE	404 (92.4%)	290 (92.9%)	200 (93.9%)	155 (95.7%)	183 (94.8%)	150 (92.6%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; TVD, Truvada

8.16.2. Sex

In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, similar percentages of male and female subjects in each group reported any AE (Table 23). Overall, no differences between sexes were apparent in the pattern of AEs reported; however, because relatively few females were enrolled in the clinical studies, firm conclusions cannot be made.

Table 23. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Number of Treatment-Emergent Adverse Events by Sex (Male or Female) (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103		ATR 236-0104, 0102		ATV/r+TVD 236-0103	
N (%)	Male (N = 675)	Female (N = 74)	Male (N = 337)	Female (N = 38)	Male (N = 316)	Female (N = 39)
Number of Subjects Experiencing any Treatment-Emergent AE	625 (92.6%)	69 (93.2%)	320 (95.0%)	35 (92.1%)	296 (93.7%)	37 (94.9%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; TVD, Truvada

8.16.3. Race

In the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, similar percentages of white and nonwhite subjects in each group reported any AE (Table 24). Overall, no differences between white and nonwhite subjects were apparent in the pattern of AEs reported.

Table 24. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Number of Treatment-Emergent Adverse Events by Race (White or Nonwhite) (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103		ATR 236-0104, 0102		ATV/r+TVD 236-0103	
N (%)	White (N = 497)	Nonwhite (N = 252)	White (N = 245)	Nonwhite (N = 130)	White (N = 277)	Nonwhite (N = 78)
Number of Subjects Experiencing any Treatment-Emergent AE	464 (93.4%)	230 (91.3%)	233 (95.1%)	122 (93.8%)	261 (94.2%)	72 (92.3%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; TVD, Truvada

8.16.4. Baseline HIV-1 RNA

In the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, similar percentages of subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL in each group reported any AE (Table 25). Overall, no differences between HIV-1 RNA subgroups were apparent in the pattern of AEs reported.

Table 25. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Number of Treatment-Emergent Adverse Events by Baseline HIV-1 RNA Level (≤ 100,000 copies/mL or > 100,000 copies/mL) (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103		ATR 236-0104, 0102		ATV/r+TVD 236-0103	
N (%)	≤ 100,000 (N = 470)	> 100,000 (N = 279)	≤ 100,000 (N = 254)	> 100,000 (N = 121)	≤ 100,000 (N = 214)	> 100,000 (N = 141)
Number of Subjects Experiencing any Treatment-Emergent AE	434 (92.3%)	260 (93.2%)	240 (94.5%)	115 (95.0%)	197 (92.1%)	136 (96.5%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; TVD, Truvada

8.16.5. Baseline CD4 Cell Count

In the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, similar percentages of subjects with baseline CD4 cell count ≤ 350 cells/μL or > 350 cells/μL in each group reported any AE (Table 26). Overall, no differences between CD4 cell count subgroups were apparent in the pattern of AEs reported.

Table 26. GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103: Number of Treatment-Emergent Adverse Events by CD4 Cell Count (≤ 350 cells/μL or > 350 cells/μL) (Pooled Safety Analysis Set)

	QUAD 236-0104, 0102, 0103		ATR 236-0104, 0102		ATV/r+TVD 236-0103	
N (%)	≤ 350 (N = 355)	> 350 (N = 394)	≤ 350 (N = 155)	> 350 (N = 220)	≤ 350 (N = 163)	> 350 (N = 192)
Number of Subjects Experiencing any Treatment-Emergent AE	328 (92.4%)	366 (92.9%)	146 (94.2%)	209 (95.0%)	154 (94.5%)	179 (93.2%)

AE, adverse event; ATR, Atripla; ATV/r, ritonavir-boosted atazanavir; CD4, cluster of differentiation 4; TVD, Truvada

8.16.6. Renal Impairment

A study with the QUAD STR in subjects with $eGFR_{CG}$ of 50 to 89 mL/min is ongoing (Study GS-US-236-0118). A brief summary of the available safety data for the 23 subjects who were enrolled as of 21 November 2011 is presented in Section 8.18.3.1.

Because clinically meaningful differences in PK of EVG or COBI were not observed in subjects at the extremes of renal function ($eGFR_{CG}$ < 30 mL/min and $eGFR_{CG}$ ≥ 90 mL/min)

investigated in Study GS-US-216-0124, dose adjustment of EVG or COBI would not be warranted in subjects with renal impairment. In addition, COBI-boosted EVG was well tolerated in the study. All AEs were Grade 1 in severity and no subjects in either renal function group prematurely discontinued study drug treatment because of an AE.

Dose-interval adjustments required for FTC and TDF in patients with CL_{cr} < 50 mL/min cannot be achieved with the fixed-dose combination QUAD tablet; therefore, QUAD should be discontinued in patients for whom CL_{cr} declines to < 50 mL/min (also see Section 8.19)

8.16.7. Hepatic Impairment

Regarding the separate components of the QUAD STR, the PK of EVG, COBI, and TFV have been studied in subjects with moderate hepatic impairment and no dose adjustment is required in these patients. The PK of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so no dose adjustment is anticipated in patients with mild to moderate hepatic impairment. The PK of the QUAD STR itself has not been studied in subjects with hepatic impairment. The safety and efficacy of QUAD have not been established in patients with significant underlying liver disorders.

The QUAD STR may be used without dose adjustment in patients with mild or moderate hepatic impairment. The QUAD STR is not recommended for use in patients with severe hepatic impairment because no data are available regarding the use of EVG or COBI in this population.

8.16.8. Coinfection with HIV-1 and Hepatitis B and/or Hepatitis C Virus

The QUAD STR is not indicated for the treatment of chronic HBV or HCV infection, and safety and efficacy have not been established in patients coinfected with HBV or HCV (as determined by HBV surface antigen serology and HCV antibody serology) and HIV-1 (TDF 300 mg per day is approved for the treatment of chronic HBV infection as a single agent). In the pooled safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, a limited number of HIV-1 infected subjects were coinfected with HBV (1.8%, 26 subjects) or HCV (4.1%, 60 subjects). The hepatic adverse reaction profile in subjects coinfected with HIV-1 and HBV or HIV-1 and HCV who received QUAD was consistent with underlying hepatitis infection. As expected in this subject population, elevations in AST and ALT occurred more frequently than in the general HIV-1 infected population.

Discontinuation of therapy with QUAD in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TDF components. Patients coinfected with HIV-1 and HBV who discontinue QUAD should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of HBV therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of HBV therapy is not

recommended because posttreatment exacerbation of hepatitis may lead to hepatic decompensation.

8.16.9. Use in Pregnancy and Lactation

No adequate and well-controlled studies of QUAD or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of EVG, COBI, FTC, or TDF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. Therefore the QUAD tablet is proposed to be assigned to Pregnancy Category B. The QUAD tablet should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

No clinically relevant concerns are apparent from review of available pregnancy data in clinical studies.

In animal studies it has been shown that EVG, COBI and TFV are excreted into milk. It is not known whether EVG or COBI are excreted into human milk. In humans, samples of breast milk obtained from 5 HIV-1 infected mothers show that FTC is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the FTC IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of FTC; TFV is secreted in human milk at low levels (estimated neonatal concentrations 128 to 266 times lower than the TFV IC_{50}). Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown. TFV-associated risks, including the risk of viral resistance to TFV, in infants breastfed by mothers being treated with TDF are unknown. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving the QUAD STR.

8.17. Postmarketing Experience

A brief summary of identified safety issues associated with the FTC and TDF components of QUAD is provided below. Pertinent guidance and/or warning statements regarding these issues are included in the proposed QUAD prescribing information.

Identified safety issues associated with the TDF component of QUAD include the following:

- Renal toxicity
- Bone events due to proximal renal tubulopathy/loss of BMD
- Interaction between didanosine and TDF (increased incidence/severity of didanosine-related adverse reactions)
- Pancreatitis

Identified safety issues associated with the FTC and TDF components of QUAD include the following:

- Lactic acidosis and severe hepatomegaly with steatosis
- Lipodystrophy
- Posttreatment hepatic flares in HIV/HBV coinfected patients (due to anti-HBV activity of FTC and TDF)

8.18. Other Additional Safety Data

A summary of cumulative safety data from the QUAD NDA safety update for the following studies is included in this section: GS-US-183-0145, GS-US-216-0105, GS-US-216-0114, and GS-US-236-0118. The data cut was 31 October 2011 for Studies GS-US-183-0145 and GS-US-216-0114 and 21 November 2011 for Studies GS-US-216-0105 and GS-US-236-0118. Safety update data for the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 (data cut: 21 November 2011) are presented with the randomized phase data.

8.18.1. EVG

8.18.1.1. Study GS-US-183-0145

GS-US-183-0145 is an ongoing Phase 3, multicenter, randomized, double-blind, double-dummy study of the safety and efficacy of EVG versus RAL, each administered with a background regimen containing a RTV-boosted PI and at least a second agent in HIV-1 infected, antiretroviral treatment-experienced adults. A total of 712 subjects received at least 1 dose of study drug (EVG, n = 354; RAL, n = 358).

In the QUAD safety update data cut, a lower percentage of subjects in the EVG group than in the RAL group reported SAEs (EVG 20.1%, 71 subjects; RAL 23.5%, 84 subjects); however, SAEs considered related to study drug were reported for similar percentages of subjects in the 2 groups (EVG 1.1%, 4 subjects; RAL 1.7%, 6 subjects). Convulsion was the only SAE considered related to study drug by the investigator that was reported for more than 1 subject in a treatment group (2 subjects in the RAL group). Twelve subjects died during the study, and death was treatment-emergent for 9 subjects (EVG 0.6%, 2 subjects; RAL 2.0%, 7 subjects); events that were the cause of death were considered related to study drug for 2 subjects in the RAL group (hemolytic anemia and cardiac arrest; deaths in EVG group were not considered related to study drug). Similar percentages of subjects in the 2 groups discontinued study drug due an AE (EVG 3.1%, 11 subjects; RAL 4.2%, 15 subjects).

8.18.2. COBI

8.18.2.1. Study GS-US-216-0105

GS-US-216-0105 is an ongoing Phase 2, randomized, double-blind, multicenter, multiple-dose, active-controlled study to assess the safety and efficacy of a regimen containing ATV/co+TVD versus ATV/r+TVD in HIV-1 infected, ARV treatment-naive adult subjects. A total of 79 subjects received at least 1 dose of study drug (ATV/co+TVD 50, ATV/r+TVD 29).

In the QUAD safety update data cut, SAEs were reported for 9 subjects (13.0%) in the All ATV/co+TVD group (ie, all subjects who received at least 1 dose of ATV/co+TVD). None of the SAEs were considered related to study drug by the investigator. One subject died due to an accidental death of unknown cause during the open-label phase of the study. This death was considered by the investigator to be not related to study drug. In the All ATV/co+TVD group in Study GS-US-216-0105, treatment-emergent AEs leading to study drug discontinuation were reported for 5 subjects (7.2%). The AEs leading to study drug discontinuation were vomiting, maculopapular rash, accidental death, and attempted suicide. In the [ATV/r→ATV/co]+TVD group, the AE that led to study drug discontinuation was decreased GFR. The vomiting and maculopapular rash were considered by the investigator to be related to study drug. The attempted suicide and accidental death were considered SAEs.

8.18.2.2. Study GS-US-216-0114

Study GS-US-216-0114 is an ongoing Phase 3, randomized double-blind, multicenter, multiple-dose, active-controlled study to evaluate the safety and efficacy ATV/co+TVD or ATV/r+TVD in HIV-1 infected, antiretroviral treatment-naive adult subjects. A total of 692 subjects received at least 1 dose of study drug (ATV/co+TVD, n = 344; ATV/r+TVD, n = 348).

In the QUAD safety update data cut (Week 48), SAEs were reported for a similar percentage of subjects in the ATV/co+TVD group compared with the ATV/r+TVD group (ATV/co+TVD 10.5%, 36 subjects; ATV/r+TVD 6.6%, 23 subjects). One SAE occurred in ≥ 1% of subjects in either treatment group (acute renal failure; 4 subjects [1.1%] in the ATV/r+TVD group). Overall, SAEs considered by the investigator to be related to study drug were infrequent in both treatment groups (ATV/co+TVD 1.5%, 5 subjects; ATV/r+TVD 1.7%, 6 subjects). No subjects died during the study. Similar percentages of subjects in both groups discontinued study drug due to an AE (ATV/co+TVD 7.3%, 25 subjects; ATV/r+TVD 7.2%, 25 subjects).

8.18.3. QUAD

8.18.3.1. Study GS-US-236-0118

Study GS-US-236-0118 is an ongoing Phase 3, open-label, multicenter, multiple-cohort study (planned N = 100) to evaluate the safety of COBI-containing highly-active antiretroviral regimens in HIV-1 infected adults with mild to moderate renal impairment.

Subjects must have an eGFR between 50 and 89 mL/min. Cohort 1 enrolled treatment-naive HIV-1 infected adult subjects with HIV-1 RNA ≥ 1000 copies/mL at screening and subjects were treated with the QUAD STR. Cohort 2 enrolled treatment-experienced HIV-1 infected adults already receiving ATV/r or DRV/r plus 2 NRTIs for at least 6 months prior to screening with HIV-1 RNA < 50 copies/mL at screening. Subjects in Cohort 2 were treated with ATV/co or COBI-boosted DRV (DRV/co) plus 2 NRTIs. As of 21 November 2011, 8 subjects have been enrolled in Cohort 1 and 15 subjects have been enrolled in Cohort 2.

In the QUAD safety update data cut, there were no SAEs or deaths. One subject (b) (6)) from Cohort 2 had an AE that led to discontinuation of study drug; the AE of "affect lability" (reported term emotional volatility) was reported to have started 2 days after the initiation of study drug and resolved without treatment 2 days after study drug was discontinued. The event was assessed as nonserious and related to study drug by the investigator.

In Cohort 1 in Study GS-US-236-0118, there was a small increase in median values for serum creatinine (baseline median 1.18 mg/dL; the median change from baseline at Week 8 was 0.11 mg/dL). The observed changes were similar to those seen in pooled QUAD group, where the eligibility criterion for eGFRCG was ≥ 70 mL/min for Studies GS-US-236-0102, GS-US-236-0103 and (eGFR) ≥ 80 mL/min for GS-US-236-0104. In Cohort 2 in Study GS-US-236-0118, there were no notable changes from baseline through Week 8 in median values for serum creatinine.

8.19. Conclusions on Safety Experience

The safety and tolerability profile of the QUAD STR for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients is supported by a robust safety database consisting of 749 HIV-1 infected subjects with a median duration of exposure to the QUAD STR of 48.4 weeks. The extent of exposure of the QUAD STR in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 is presented in Section 8.2. A brief summary of AEs reported in the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 is provided in Table 19.

The QUAD STR was well tolerated, as demonstrated by the low number of AEs leading to study drug discontinuation (3.5%, 26 of 749 subjects) and also by the fact that most AEs were mild to moderate in severity. There were low overall incidences of treatment-emergent death and serious adverse events (SAEs). The most frequently reported AEs for QUAD were diarrhea, nausea, and headache. Subgroup analyses of AEs by baseline characteristics of sex, age, race, and HIV baseline characteristics of viral load and CD4 cell count showed no clinically meaningful differences between subgroups. Data for EVG in antiretroviral treatment-experienced subjects and for COBI as a booster of ATV in antiretroviral treatment-naive subjects also support the favorable safety and tolerability profiles of these agents (Section 8.18).

Similar percentages of subjects in the QUAD, Atripla, and ATV/r+TVD groups reported any SAE (QUAD 9.2%, 69 of 749 subjects; Atripla 6.7%, 25 of 375 subjects; ATV/r+TVD 8.7%, 31 of 355 subjects).

Phase 1 Study GS-US-216-0121 showed that COBI administration resulted in small reversible increases in serum creatinine without affecting actual renal glomerular filtration rate as assessed via iohexol clearance (Section 5.1.3.2.2). Serum creatinine is cleared by the kidney through a combination of glomerular filtration and active secretion. Active tubular secretion is a minor component of the clearance of creatinine, accounting for 10% to 40% in patients with normal renal function with greater variability in patients with chronic kidney disease {11602}, {10070}, {11576}. Similar to other commonly used drugs including cimetidine and trimethoprim {18704}, COBI has been found to be associated with reversible increase in serum creatinine without affecting actual glomerular filtration rate, likely via an inhibition of renal OCT2 and MATE1. As expected based on the results of Study GS-US-216-0121, small increases in serum creatinine, which led to small decreases in $eGFR_{CG}$, were also observed in subjects who received QUAD in the Phase 3 studies. The changes were noted as early as Week 2 of treatment, with only minimal changes after Week 4. However, no decreases in cystatin C clearance, a marker of glomerular filtration, were observed in these studies. Because the small initial increase in serum creatinine and initial reduction in eGFR is predictable after QUAD initiation, serum creatinine and eGFR are still adequate tests to monitor renal function in patients initiating QUAD.

Six subjects discontinued in the QUAD group (< 1%) and 1 subject discontinued in the ATV/r+TVD group due to renal events (Appendix 5). Of the 6 subjects in the QUAD group:

- 2 subjects had small increases (~0.2 to 0.3 mg/dL) in serum creatinine without tubular dysfunction within weeks of initiation the QUAD STR. For 1 subject, serum creatinine levels returned to baseline after study drug discontinuation, reflecting the effect of COBI on serum creatinine. For the other subject, serum creatinine levels improved but did not return to baseline due to the subject switching to an RTV-boosted PI regimen.

- 2 subjects had rapid increases in serum creatinine with tubular dysfunction within a few weeks of initiation the QUAD STR. For both subjects, renal abnormalities improved or resolved soon after discontinuation of the QUAD STR. Both subjects had either screening or baseline eGFR < 70 mL/min and violated the study protocol because the subjects were not discontinued from QUAD when their eGFR decreased below 50 mL/min (per protocol-defined stopping rules based on prescribing information for FTC and TDF).

- 2 subjects showed slow and gradual increases in serum creatinine with tubular dysfunction over months after initiation with the QUAD STR, which improved after discontinuation of study drug.

Five out of the 6 subjects in the QUAD group had evidence of renal impairment at baseline (GFR < 90 mL/min or at least 1+ proteinuria). The type of renal adverse reactions seen in the QUAD Phase 3 studies have been reported with the use of TDF, as described in labeling for all approved TDF-containing products (ie, Viread, Truvada, Atripla, and Complera). The rate of reported renal AEs leading to discontinuations with the QUAD STR was consistent with the rate reported in studies using a RTV-boosted PI along with a TDF-based background regimen (Section 8.7.1).

In the QUAD safety update data cut (21 November 2011) for Studies GS-US-236-0102, GS-US-236-0103, an additional subject (b) (6)) discontinued QUAD therapy due to an AE of increased blood creatinine. After discontinuation of QUAD, the subject's laboratory values returned to baseline values (Appendix 5).

Appropriate guidance is included in the proposed QUAD prescribing information to reduce the risk for development of renal events. It is recommended that CL_{cr} is assessed in all patients prior to initiating therapy with QUAD. The QUAD STR should not be initiated patients with CL_{cr} < 70 mL/min (the cutoff used in Phase 3 studies of QUAD). Routine monitoring of CL_{cr} and serum phosphorus should be performed during therapy with QUAD in patients with renal impairment and in patients at risk for renal impairment. Dose-interval adjustments required for FTC and TDF in patients with $eGFR_{CG}$ < 50 mL/min cannot be achieved with the fixed-dose combination QUAD tablet; therefore, QUAD should be discontinued in patients for whom $eGFR_{CG}$ declines to < 50 mL/min. Patients with confirmed changes in serum creatinine ≥ 0.4 mg/dL from baseline may be at increased risk of TDF-related renal toxicity and should be monitored more frequently.

Clinically relevant bone abnormalities have not been seen with TDF in long-term (> 3 years) clinical studies in HIV-1 infected adults, and were not seen over 48 weeks in the studies with QUAD. In Study GS-US-236-0103, there were comparable decreases in baseline BMD at the lumbar spine and hip in the QUAD group compared with the ATV/r+TVD group (changes at Week 48: spine –2.63% in the QUAD group vs –3.33% in the ATV/r+TVD group; hip –3.06% in the QUAD group vs –3.88% in the ATV/r+TVD group).

The QUAD STR demonstrated a favorable safety profile with clinically relevant tolerability advantages over both Atripla and ATV/r+TVD as follows:

- Treatment-emergent Grade 4 laboratory abnormalities were reported less frequently in the QUAD group than in the Atripla group or the ATV/r+TVD group: QUAD 3.9% of subjects with maximum Grade 4 abnormalities; Atripla 9.7% of subjects with maximum Grade 4 abnormalities; and ATV/r+TVD 15.9% of subjects with maximum Grade 4 abnormalities.

- In the pooled safety analysis set in Studies GS-US-236-0102 and GS-US-236-0103, mean increases from baseline through Week 48 in fasting total cholesterol and LDL cholesterol were lower for the QUAD group compared with the Atripla group. Mean increases from baseline through Week 48 in fasting triglycerides were lower for the QUAD group compared with the ATV/r+TVD group.

- In the pooled safety analysis set in Studies GS-US-236-0104 and GS-US-236-0102, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported a neurological/psychiatric AE based on a prespecified analysis (QUAD 42.9%, 170 subjects; Atripla 62.1%, 233 subjects).

- In the pooled safety analysis set in Studies GS-US-236-0104 and GS-US-236-0102, a significantly lower percentage of subjects in the QUAD group compared with the Atripla group reported any rash AE based on a prespecified analysis (QUAD 17.5%, 131 subjects; Atripla 27.7%, 104 subjects).

- Lower percentages of subjects in the QUAD group than in the ATV/r+TVD group had graded abnormalities of ALT and AST.

- The renal safety profile of QUAD STR is consistent with the known and manageable renal toxicity associated with the use of TDF.

In conclusion, the QUAD STR was well tolerated with a safety profile that compares favorably with those of current US DHHS-preferred NNRTI- and PI-based regimens in HIV-1 infected subjects.

9. CONCLUSIONS ON THE OVERALL BENEFIT-RISK PROFILE

The need remains for new therapeutic options for patients infected with HIV-1 that demonstrate potent and sustained efficacy with favorable tolerability and minimal long-term toxicity combined with practical and convenient dosing regimens. The most significant challenge in achieving long-term virologic suppression is the avoidance of drug resistance. Incomplete or partial adherence to treatment regimens is a critical factor contributing to the development of resistance and treatment failure. Studies with other medicinal products have shown that a once-daily STR significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {13840}, {15302}, {15951}, {15415}. Studies have shown that a once-daily STR significantly improved adherence, treatment satisfaction, and virologic outcomes for patients infected with HIV-1 {13840}, {15302}, {15951}, {15415}.The development of STRs is a strategy employed to simplify treatment and thereby improve adherence to therapy in order to achieve better rates of virologic suppression, resulting in improved long-term outcomes in patients with HIV infection.

The following considerations support a favorable benefit/risk profile for the QUAD STR for the treatment of adult HIV-1 infected patients.

Benefits

The QUAD STR has demonstrated potent, durable, and rapid antiretroviral activity, along with a favorable safety and tolerability profile. The QUAD application is supported by 3 well-designed, randomized, active-controlled, double-dummy studies comparing the QUAD STR versus US DHHS-preferred regimens using a noninferiority design (in Phase 3): one Phase 2 study (GS-US-236-0104), and two Phase 3 studies (GS-US-236-0102 and GS-US-236-0103). In all 3 studies, the virologic response rates of both the QUAD and the comparator groups were among the highest seen in clinical studies in antiretroviral treatment-naive HIV-1 infected adults. The efficacy results from these 3 studies were robust and highly consistent across studies and endpoints that compared the QUAD STR versus both NNRTI (Atripla) and PI (ATV/r+TVD) US DHHS-preferred antiretroviral-treatment regimens. Nearly all subgroup analyses revealed point estimates that favored the QUAD STR over the comparator regardless of demographics and disease baseline characteristics.

Immunologic benefits of treatment were demonstrated by increases in CD4 cell counts. The difference in the change in CD4 cell count from baseline to Week 48 was in favor of QUAD versus Atripla in Study GS-US-236-0102.

The frequency of resistance development in subjects taking the QUAD STR was low and comparable with that of the other first-line regimens Atripla and ATV/r+TVD. Treatment with the QUAD STR will preserve use of NNRTI- and PI-based regimens for INSTI failures with resistance.

In addition to high rates of virologic suppression, the QUAD STR demonstrated a favorable safety and tolerability profile with clinically relevant tolerability advantages over both Atripla and ATV/r+TVD. These include improved lipid parameters. In addition, there was a lower incidence of neurological and psychiatric AEs and rash AEs for QUAD versus Atripla, and a lower incidence of liver-related laboratory abnormalities and bilirubin-related AEs for QUAD versus ATV/r+TVD. A further benefit of QUAD (proposed Pregnancy Category B) over Atripla (Pregnancy Category D) is that due to the teratogenicity potential of the EFV component, Atripla is not recommended in women of childbearing potential who wish to become pregnant.

The clinical safety database is robust and includes long-term data originating from the individual components of QUAD as well as clinical safety data for the QUAD STR. The primary sources of QUAD STR safety data are Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103, which support the favorable safety and tolerability of QUAD in antiretroviral treatment-naive subjects. Most AEs in subjects treated with QUAD were mild to moderate, with low rates of SAEs and AEs leading to study drug discontinuation. The most frequently reported AEs for QUAD were diarrhea, nausea, and headache, most of which were mild, occurred early, resolved while continuing on study drug, and rarely led to study drug discontinuation. Subgroup analyses of AEs by baseline demographics and HIV-1 characteristics showed no meaningful safety differences.

The QUAD STR combines an INSTI, EVG boosted by COBI, with the standard of care, US DHHS-preferred dual NRTI/NtRTI backbone of FTC/TDF (Truvada), in a once-daily tablet. At this time, RAL is the only INSTI approved for use in adults in the US. RAL requires twice-daily dosing, a regimen recently confirmed by the early termination of a study (QDMRK study) comparing once-daily with twice-daily RAL use that showed a lower response rate, higher VF, and higher resistance in subjects with viral loads > 100,000 copies/mL when administered once daily {19639}.

Extensive postmarketing experience with FTC (~3 million patient-years) and TDF (~5 million patient-years) supports the proposed use of the QUAD STR for the treatment of HIV-1 infection in adults. Pending regulatory approval, QUAD would be the first INSTI based STR for the treatment of HIV-1 infection.

Risks

Surveillance of postmarketing spontaneous AE reports has provided evidence that TDF therapy may cause renal adverse reactions. These reactions include renal failure (including acute renal failure), Fanconi syndrome, proximal renal tubulopathy, acute tubular necrosis, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, and polyuria. TDF-associated renal toxicity is thought to be mainly due to an effect on proximal renal tubules. Although the molecular mechanism is not fully understood, it is plausible that renal toxicity might be a consequence of disrupted transport equilibrium between the tubular uptake and efflux of TFV due to genetic polymorphism in renal transporters.

Serum creatinine is cleared by the kidney through a combination of glomerular filtration and active secretion. Active tubular secretion is a minor component of the renal elimination of creatinine, accounting for 10% to 40% of its clearance in patients with normal renal function {11602}, {10070}, {11576}. COBI inhibits active secretion of creatinine, thereby leading to small creatinine elevations. COBI does not affect glomerular function (Section 5.1.3.2.2). Therefore, small increases in serum creatinine are expected after initiation of QUAD that result in decreases of approximately 15 mL/min in eGFR, but not aGFR. This inhibition of creatinine secretion is seen for other commonly used drugs such as cimetidine and trimethoprim {18704}.

In Studies GS-US-236-0104, GS-US-236-0102 and GS-US-236-0103, 8 subjects discontinued study drug due to renal AEs, 7 on QUAD [1 subject discontinued after the NDA data cut], and 1 on ATV/r+TVD group. Of the 7 subjects who discontinued QUAD therapy due to renal AEs, 5 had evidence of renal impairment at baseline. In addition, 6 subjects discontinued study drug due to renal events in Studies GS-US-215-0105 and GS-US-216-0114 following administration of COBI as a pharmacoenhancer of ATV in combination with Truvada (TDF/FTC). Overall, a total of 13/1143 subjects (1%) discontinued a COBI+TDF containing regimen due to a renal event; this was consistent with the rate seen in the comparator regimens containing TDF with a boosted PI (7/732, 1%). The renal laboratory abnormalities were improved upon discontinuation of QUAD or ATV/co+TVD. The renal AEs leading to study drug discontinuation were consistent with postmarketing data in labels for TDF-containing products, and with rates in published clinical studies of TDF (Section 8.7.1).

Appropriate guidance is included in the proposed QUAD prescribing information to reduce the risk for development of renal events. It is recommended that CL_{cr} is assessed in all patients prior to initiating therapy with QUAD. QUAD should not be initiated patients with $CL_{cr} < 70$ mL/min (the cutoff used in Phase 3 studies of QUAD). Routine monitoring of CL_{cr} and serum phosphorus should be performed during therapy with QUAD in patients with renal impairment and in patients at risk for renal impairment. Dose-interval adjustments required for FTC and TDF in patients with $eGFR_{CG} < 50$ mL/min cannot be achieved with the fixed-dose combination QUAD tablet; therefore, QUAD should be discontinued in patients for whom $eGFR_{CG}$ declines to < 50 mL/min. Patients with confirmed changes in serum creatinine ≥ 0.4 mg/dL from baseline may be at increased risk of TDF-related renal toxicity and should be monitored more frequently.

The QUAD STR may increase the plasma concentrations of drugs metabolized by CYP3A. The potential for clinically significant drug-drug interactions with narrow therapeutic index drugs that are highly dependent on CYP3A for their clearance are included as contraindications for use with the QUAD STR. The QUAD STR is proposed for use as a complete regimen for the treatment of antiretroviral treatment-naive HIV-1 infection in adults and is not recommended for use with other antiretroviral agents. The QUAD STR should not be used in conjunction with PIs or NNRTIs due to potential drug-drug interactions, including altered and/or suboptimal PK of EVG, COBI, and/or the coadministered antiretroviral products.

Clinically relevant bone abnormalities have not been seen in long-term (> 3 years) clinical studies in HIV-1 infected adults with TDF, and were not seen over 48 weeks in the studies with the QUAD STR. In Study GS-US-236-0103, there were comparable decreases in baseline BMD at the lumbar spine and hip in the QUAD group compared with the ATV/r+TVD group. Postmarketing reports indicate that bone abnormalities (infrequently contributing to fractures) may be associated with TDF use. If bone abnormalities are suspected, appropriate consultation should be obtained.

The principal warnings or precautions applicable to FTC and TDF include lactic acidosis and severe hepatomegaly with steatosis and use in patients coinfected with chronic HBV infection. The QUAD STR is not indicated for the treatment of chronic HBV or HCV infection, and safety and efficacy have not been established in patients coinfected with HBV or HCV and HIV-1. Discontinuation of therapy with QUAD in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the anti-HBV activity of the FTC and TDF components.

Conclusion

The QUAD STR has demonstrated both potent and durable antiviral efficacy with a safety and tolerability profile that offers an alternative with advantages over the currently recommended first-line NNRTI- and PI-based antiretroviral regimens. The QUAD STR is the first fixed-dose combination containing an HIV integrase-strand transfer inhibitor for use once daily in the treatment of HIV-1 infection. The QUAD STR has a favorable benefit/risk profile and represents a new therapeutic option for HIV-1 infected adults who are antiretroviral treatment-naive or have no known substitutions associated with resistance to the individual components.

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11. APPENDICES

Appendix 1. US Prescribing Information for Truvada (Emtricitabine/Tenofovir DF)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRUVADA safely and effectively. See full prescribing information for TRUVADA.

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets

Initial U.S. Approval: 2004

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA. (5.1)**
- **TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued TRUVADA. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.2)**

----------**RECENT MAJOR CHANGES**----------

Indications and Usage (1)	7/2011
Dosage and Administration (2.1, 2.2)	7/2011
Warnings and Precautions	
Decreases in Bone Mineral Density (5.5)	7/2011

----------**INDICATIONS AND USAGE**----------

TRUVADA, a combination of EMTRIVA and VIREAD, both nucleoside analog HIV-1 reverse transcriptase inh bitors, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. (1)

----------**DOSAGE AND ADMINISTRATION**----------

- Recommended dose in adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg): One tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1)
- Dose recommended in renal impairment:
  Creatinine clearance 30-49 mL/min: 1 tablet every 48 hours. (2.2)
  CrCl below 30 mL/min or hemodialysis: Do not use TRUVADA. (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------

Tablets: 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. (3)

----------**CONTRAINDICATIONS**----------

None. (4)

----------**WARNINGS AND PRECAUTIONS**----------

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with TRUVADA. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering Truvada with concurrent or recent use of nephrotoxic drugs. (5.3)
- Coadministration with Other Products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate including ATRIPLA, EMTRIVA, VIREAD; or with drugs containing lamivudine. Do not administer in combination with HEPSERA. (5.4)
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (5.6)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.7)
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification. (5.8)

----------**ADVERSE REACTIONS**----------

Most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------**DRUG INTERACTIONS**----------

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.1)
- Atazanavir: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with TRUVADA only with ritonavir; monitor for evidence of tenofovir toxicity. (7.2)
- Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity. (7.2)

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: pregnancy registry available: Enroll patients by calling 1-800-258-4263.
- Nursing mothers: Women infected with HIV should be instructed not to breast feed. (8.3)
- Pediatrics: Safety and efficacy not established in patients less than 12 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, in combination with other antiretrovirals *[See Warnings and Precautions (5.1)]*.

TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUVADA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued TRUVADA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

TRUVADA®, a combination of EMTRIVA® and VIREAD®, is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- TRUVADA should not be coadministered with ATRIPLA®, EMTRIVA, VIREAD or lamivudine-containing products *[See Warnings and Precautions (5.4)]*.
- In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history *[See Clinical Pharmacology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The dose of TRUVADA for adults and pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg (greater than or equal to 77 lb) is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

2.2 Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when EMTRIVA or VIREAD were administered to subjects with moderate to severe renal impairment *[see EMTRIVA or VIREAD Package Insert]*. Therefore, the dosing interval of TRUVADA should be adjusted in patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 1. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients *[See Warnings and Precautions (5.3)]*.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment *[See Warnings and Precautions (5.3)]*.

Table 1 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[a]		
	≥50	**30–49**	**<30 (Including Patients Requiring Hemodialysis)**
Recommended Dosing Interval	Every 24 hours	Every 48 hours	TRUVADA should not be administered.

a. Calculated using ideal (lean) body weight

No data are available to make dose recommendations in pediatric patients 12 years of age and older with renal impairment.

3 DOSAGE FORMS AND STRENGTHS

TRUVADA is available as tablets. Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil). The tablets are blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side and with “701” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TRUVADA should be

suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. TRUVADA is not approved for the treatment of chronic HBV infection and the safety and efficacy of TRUVADA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued TRUVADA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are coinfected with HIV-1 and HBV should be closely monitored with both clinical and laboratory follow up for at least several months after stopping treatment with Truvada. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

5.3 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD *[See Adverse Reactions (6.2)]*.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with TRUVADA. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment, including patients who have previously experienced renal events while receiving HEPSERA.

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with creatinine clearance 30–49 mL/min, *[See Dosage and Administration (2.2)]*. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with creatinine clearance below 30 mL/min or patients requiring hemodialysis.

TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent.

5.4 Coadministration with Other Products

TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. TRUVADA should not be coadministered with ATRIPLA, EMTRIVA, or VIREAD. Due to similarities between emtricitabine and lamivudine, TRUVADA should not be coadministered with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

TRUVADA should not be administered with HEPSERA® (adefovir dipivoxil).

5.5 Decreases in Bone Mineral Density

Assessment of bone mineral density (BMD) should be considered for HIV-1 infected adults and pediatric patients 12 years of age and older who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Tenofovir Disoproxil Fumarate: In a 144-week trial of treatment-naive adult subjects, decreases in BMD were seen at the lumbar spine and hip in both arms of the trial. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz compared with subjects receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through 144 weeks. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the comparator subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the comparator group. Tenofovir disoproxil fumarate was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD.

In a clinical trial of HIV-1 infected pediatric subjects 12 years of age and older (Study 321), bone effects were similar to adult subjects. Under normal circumstances BMD increases rapidly in this age group. In this trial, the mean rate of bone gain was less in the VIREAD-treated group compared to the placebo group. Six VIREAD treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss in 48 weeks. Among 28 subjects receiving 96 weeks of VIREAD, Z-scores declined by -0.341 for lumbar spine and -0.458 for total body. Skeletal growth (height) appeared to be unaffected. Markers of bone turnover in VIREAD-treated pediatric subjects 12 years of age and older suggest increased bone turnover, consistent with the effects observed in adults.

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the VIREAD prescribing information.

Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of VIREAD *[See Adverse Reactions (6.2)]*.

5.6 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral

therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRUVADA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

5.8 Early Virologic Failure

Clinical trials in HIV-infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virological failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis *[See Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe Acute Exacerbations of hepatitis B *[See Boxed Warning, Warnings and Precautions (5.2)]*.
- New Onset or Worsening Renal Impairment *[See Warnings and Precautions (5.3)]*.
- Decreases in Bone Mineral Density *[See Warnings and Precautions (5.5)]*.
- Immune Reconstitution Syndrome *[See Warnings and Precautions (5.7)]*.

6.1 Adverse Reactions from Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Subjects

The most common adverse reactions (incidence greater than or equal to 10%, any severity) occurring in Study 934, an active-controlled clinical trial of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also Table 2 for the frequency of treatment-emergent adverse reactions (Grade 2–4) occurring in greater than or equal to 5% of subjects treated with efavirenz, emtricitabine, and tenofovir disoproxil fumarate in this trial.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naive subjects received either VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in other trials in treatment-experienced or treatment-naive subjects receiving VIREAD and/or EMTRIVA (Table 2).

Table 2 Selected Treatment-Emergent Adverse Reactions[a] (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[b]	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event[c]	7%	9%

a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

b. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

Laboratory Abnormalities: Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of VIREAD and/or EMTRIVA (Table 3).

Table 3 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

	FTC + TDF + EFV[a]	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8.0 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (≥3+)	<1%	1%
Neutrophils (<750/mm^3)	3%	5%
Fasting Triglycerides (>750 mg/dL)	4%	2%

a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

In addition to the events described above for Study 934, other adverse reactions that occurred in at least 5% of subjects receiving EMTRIVA or VIREAD with other antiretroviral agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, and rhinitis.

In addition to the laboratory abnormalities described above for Study 934, Grade 3/4 laboratory abnormalities of increased bilirubin (>2.5 x ULN), increased pancreatic amylase (>2.0 x ULN), increased or decreased serum glucose (<40 or >250 mg/dL), and increased serum lipase (>2.0 x ULN) occurred in up to 3% of subjects treated with EMTRIVA or VIREAD with other antiretroviral agents in clinical trials.

Clinical Trials in Pediatric Subjects 12 Years of Age and Older

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with EMTRIVA in the

larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, please consult the EMTRIVA prescribing information.

Tenofovir Disoproxil Fumarate: In a pediatric clinical trial conducted in subjects 12 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults *[See Warnings and Precautions (5.5)].*

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIREAD. No additional adverse reactions have been identified during postapproval use of EMTRIVA. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, *and Mediastinal Disorders*
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders
rash

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions
asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

No drug interaction trials have been conducted using TRUVADA tablets. Drug interaction trials have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of TRUVADA. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate *[See Clinical Pharmacology (12.3)]*.

7.1 Didanosine

Coadministration of TRUVADA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When tenofovir disoproxil fumarate was administered with didanosine the C_{max} and AUC of didanosine administered as either the buffered or enteric-coated formulation increased significantly *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of $CD4^+$ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with TRUVADA should be under fasted conditions.

7.2 Atazanavir

Atazanavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving atazanavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.

Tenofovir decreases the AUC and C_{min} of atazanavir *[See Clinical Pharmacology (12.3)]*. When coadministered with TRUVADA, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with TRUVADA.

7.3 Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations *[See Clinical Pharmacology (12.3)]*. The mechanism of this interaction is unknown. Patients receiving lopinavir/ritonavir and TRUVADA should be monitored for TRUVADA-associated adverse reactions. TRUVADA should be discontinued in patients who develop TRUVADA-associated adverse reactions.

7.4 Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion *[See Clinical Pharmacology (12.3)]*. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir. Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Emtricitabine: The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate: Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

There are, however, no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, TRUVADA should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. It is not known whether emtricitabine is excreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving TRUVADA**.

8.4 Pediatric Use

Truvada should only be administered to pediatric patients 12 years of age and older with body weight greater than or equal to 35 kg (greater than or equal to 77 lb) because it is a fixed-dose combination tablet containing a component, VIREAD, for which safety and efficacy have not been established in pediatric patients less than 12 years of age or weighing less than 35 kg (less than 77 lb) *[See Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical trials of EMTRIVA or VIREAD did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Impaired Renal Function

It is recommended that the dosing interval for TRUVADA be modified in patients with creatinine clearance 30–49 mL/min. TRUVADA should not be used in patients with creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis *[See Dosage and Administration (2.2)]*.

10 OVERDOSAGE

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology trials single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one trial, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

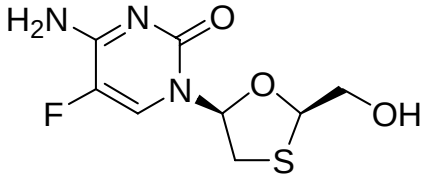
Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

TRUVADA tablets are fixed dose combination tablets containing emtricitabine and tenofovir disoproxil fumarate. EMTRIVA is the brand name for emtricitabine, a synthetic nucleoside analog of cytidine. Tenofovir disoproxil fumarate (tenofovir DF) is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

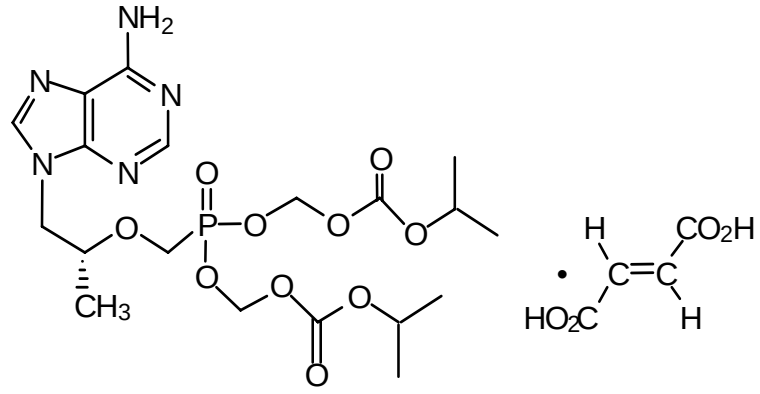
Emtricitabine: The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25 °C. The partition coefficient (log p) for emtricitabine is -0.43 and the pKa is 2.65.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir disoproxil fumarate is 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

TRUVADA tablets are for oral administration. Each film-coated tablet contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, (which is equivalent to 245 mg of tenofovir disoproxil), as active ingredients. The tablets also include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, please consult the EMTRIVA and VIREAD prescribing information.

12.1 Mechanism of Action

TRUVADA is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate. *[See Clinical Pharmacology (12.4)].*

12.3 Pharmacokinetics

TRUVADA: One TRUVADA tablet was bioequivalent to one EMTRIVA capsule (200 mg) plus one VIREAD tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 4. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 4. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.

Table 4 Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults[a]

	Emtricitabine	Tenofovir
Fasted Oral Bioavailability[b] (%)	92 (83.1–106.4)	25 (NC–45.0)
Plasma Terminal Elimination Half-Life[b] (hr)	10 (7.4–18.0)	17 (12.0–25.7)
C_{max}[c] (µg/mL)	1.8 ± 0.72[d]	0.30 ± 0.09
AUC[c] (µg·hr/mL)	10.0 ± 3.12[d]	2.29 ± 0.69
CL/F[c] (mL/min)	302 ± 94	1043 ± 115
CL_{renal}[c] (mL/min)	213 ± 89	243 ± 33

a. NC = Not calculated

b. Median (range)

c. Mean (± SD)

d. Data presented as steady state values.

Effects of Food on Oral Absorption

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. The mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, VIREAD (tenofovir) was taken under fed conditions. Emtricitabine systemic exposures (AUC and C_{max}) were unaffected when TRUVADA was administered with either a high fat or a light meal.

Special Populations

Race

Emtricitabine: No pharmacokinetic differences due to race have been identified following the administration of EMTRIVA.

Tenofovir Disoproxil Fumarate: There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of VIREAD.

Gender

Emtricitabine and Tenofovir Disoproxil Fumarate: Emtricitabine and tenofovir pharmacokinetics are similar in male and female subjects.

Pediatric Patients

TRUVADA should not be administered to pediatric patients less than 12 years of age or weighing less than 35 kg (less than 77 lb).

Emtricitabine: The pharmacokinetics of emtricitabine at steady state were determined in 27 HIV-1-infected pediatric subjects 13 to 17 years of age receiving a daily dose of 6 mg/kg up to a maximum dose of 240 mg oral solution or a 200 mg capsule; 26 of 27 subjects in this age group received the 200 mg EMTRIVA capsule. Mean (± SD) C_{max}

and AUC were 2.7 ± 0.9 µg/mL and 12.6 ± 5.4 µg•hr/mL, respectively. Exposures achieved in pediatric subjects 12 to less than 18 years of age were similar to those achieved in adults receiving a once daily dose of 200 mg.

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/mL and 3.39 ± 1.22 µg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment *[See Warnings and Precautions (5.3)]*. In adult subjects with creatinine clearance below 50 mL/min, C_{max}, and $AUC_{0-\infty}$ of emtricitabine and tenofovir were increased. It is recommended that the dosing interval for TRUVADA be modified in patients with creatinine clearance 30–49 mL/min. TRUVADA should not be used in patients with creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis *[See Dosage and Administration (2.2)]*.

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of TRUVADA or emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Assessment of Drug Interactions

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

In vitro studies and clinical pharmacokinetic drug-drug interaction trials have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir disoproxil fumarate, and zidovudine (see Tables 5 and 6). Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and abacavir, efavirenz, emtricitabine, entecavir, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, saquinavir/ritonavir, and tacrolimus in trials conducted in healthy volunteers (see Tables 7 and 8).

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	⇔	⇔	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers.

b. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 6 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[b] (90% CI)		
				C_{max}	AUC	C_{min}
Tenofovir DF	300 once daily × 7 days	200 once daily × 7 days	17	⇔	⇔	⇔
Zidovudine	300 twice daily × 7 days	200 once daily × 7 days	27	↑ 17 (↑ 0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	⇔
Indinavir	800 × 1	200 × 1	12	⇔	⇔	NA
Famciclovir	500 × 1	200 × 1	12	⇔	⇔	NA
Stavudine	40 × 1	200 × 1	6	⇔	⇔	NA

a. All interaction trials conducted in healthy volunteers.

b. ↑ = Increase; ↓ = Decrease; ⇔ = No Effect; NA = Not Applicable

Table 7 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[a] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[b] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Atazanavir[c]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily × 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	↑ 13 (↑ 1 to ↑ 27)	⇔	⇔

a. Subjects received VIREAD 300 mg once daily.

b. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated

c. Reyataz Prescribing Information

Table 8 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Tenofovir

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[a] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Atazanavir[b]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[b]	Atazanavir/Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[c] (↓ 42 to ↓ 3)	↓ 23[c] (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Entecavir	1 mg once daily x 10 days	28	⇔	↑ 13 (↑ 11 to ↑ 15)	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Methadone[d]	40-110 once daily × 14 days[e]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1250 twice daily × 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[f]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) Once daily × 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑41) ⇔	↑ 29[g] (↑ 12 to ↑ 48) ⇔	↑ 47[g] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)
Tacrolimus	0.05 mg/kg twice daily x 7 days	21	⇔	⇔	⇔

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

d. R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD.

e. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.

f. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.

g. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous trials, indicating lack of clinically significant drug interactions between these agents and VIREAD.

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Table 9 summarizes the effects of tenofovir disoproxil fumarate on the pharmacokinetics of didanosine. Concomitant dosing of tenofovir disoproxil fumarate with didanosine buffered tablets or enteric-coated capsules significantly increases the C_{max} and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. See *Drug Interactions (7.1)* regarding use of didanosine with VIREAD.

Table 9 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine[a] Dose (mg)/Method of Administration[a]	VIREAD Method of Administration[a]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[b]	
			C_{max}	AUC
Buffered tablets				
400 once daily[c] x 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hours after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

a. Administration with food was with a light meal (~373 kcal, 20% fat).

b. Increase = ↑; Decrease = ↓; No Effect = ⇔

c. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

12.4 Microbiology

Mechanism of Action

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5′-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Emtricitabine and Tenofovir Disoproxil Fumarate: In combination studies evaluating the cell culture antiviral activity of emtricitabine and tenofovir together, synergistic antiviral effects were observed.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) values for emtricitabine were in the range of 0.0013–0.64 μM (0.0003–0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007–1.5 μM).

Tenofovir Disoproxil Fumarate: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC_{50} values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 5.5 μM).

Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

In a clinical trial of treatment-naive subjects *[Study 934, see Clinical Studies (14.1)]*, resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subjects isolates in the EMTRIVA + VIREAD group and in 10/29 analyzed subjects isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

Emtricitabine: Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and in vivo. Genotypic analysis of these isolates showed that the reduced

susceptibility to emtricitabine was associated with a substitution in the HIV-1 RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Tenofovir Disoproxil Fumarate: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In treatment-naive subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the VIREAD arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing VIREAD through Week 96 showed greater than 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a substitution in the HIV-1 RT gene resulting in the K65R amino acid substitution.

Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either lamivudine or emtricitabine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

Emtricitabine: Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained susceptibility in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

Tenofovir Disoproxil Fumarate: HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at

doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

Clinical Study 934 supports the use of TRUVADA tablets for the treatment of HIV-1 infection. Additional data in support of the use of TRUVADA are derived from

Study 903, in which lamivudine and tenofovir disoproxil fumarate (tenofovir DF) were used in combination in treatment-naive adults, and clinical Study 303 in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these trials, please consult the prescribing information for tenofovir DF and emtricitabine.

14.1 Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naive subjects. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline $CD4^+$ cell count was 245 cells/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Subjects were stratified by baseline $CD4^+$ cell count (< or ≥200 cells/mm^3); 41% had $CD4^+$ cell counts <200 cells/mm^3 and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 10.

Table 10 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)

Outcomes	At Week 48		At Week 144	
	FTC + TDF + EFV (N=244)	AZT/3TC + EFV (N=243)	FTC + TDF + EFV (N=227)[a]	AZT/3TC + EFV (N=229)[a]
Responder[b]	84%	73%	71%	58%
Virologic failure[c]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons[d]	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to

adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in $CD4^+$ cell count was 190 cells/mm^3 in the emtricitabine + tenofovir DF group and 158 cells/mm^3 in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm^3 at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir DF group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

16 HOW SUPPLIED/STORAGE AND HANDLING

The blue, capsule-shaped, film-coated, tablets contain 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil), are debossed with “GILEAD” on one side and with “701” on the other side, and are available in unit of use bottles (containing a dessicant [silica gel canister or sachet] and closed with a child-resistant closure) of:

- 30 tablets (NDC 61958-0701-1)

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

- Keep container tightly closed
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing.

17 PATIENT COUNSELING INFORMATION and FDA-APPROVED PATIENT LABELING

Information for Patients

Patients should be advised that:

- TRUVADA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using TRUVADA.
- The use of TRUVADA has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.
- The long term effects of TRUVADA are unknown.
- TRUVADA tablets are for oral ingestion only.
- It is important to take TRUVADA with combination therapy on a regular dosing schedule to avoid missing doses.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA should be suspended in any patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) *[See Warnings and Precautions (5.1)]*.
- All patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating antiretroviral therapy.
- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued TRUVADA.
- Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent *[See Warnings and Precautions (5.3)]*. Dosing interval of TRUVADA may need adjustment in patients with renal impairment *[See Dosage and Administration (2.2)]*.
- TRUVADA should not be coadministered with ATRIPLA, EMTRIVA, or VIREAD; or with drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) *[See Warnings and Precautions (5.4)]*.
- TRUVADA should not be administered with HEPSERA *[See Warnings and Precautions (5.4)]*.
- Decreases in bone mineral density have been observed with the use of VIREAD. Bone monitoring should be considered in patients who have a history of pathologic bone fracture or at risk for osteopenia *[See Warnings and Precautions (5.5)].*

FDA-Approved Patient Labeling

TRUVADA® (tru-VAH-dah) tablets

Generic name: emtricitabine and tenofovir disoproxil fumarate
(em tri SIT uh bean and te NOE' fo veer dye soe PROX il FYOU mar ate)

Read the Patient Information that comes with TRUVADA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. You should stay under a healthcare provider's care when taking TRUVADA. **Do not change or stop your medicine without first talking with your healthcare provider**. Talk to your healthcare provider or pharmacist if you have any questions about TRUVADA.

What is the most important information I should know about TRUVADA?

- **Some people who have taken medicine like TRUVADA (nucleoside analogs) have developed a serious condition called lactic acidosis** (build up of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your healthcare provider right away if you get the following signs or symptoms of lactic acidosis.**
  - You feel very weak or tired.
  - You have unusual (not normal) muscle pain.
  - You have trouble breathing.
  - You have stomach pain with nausea and vomiting.
  - You feel cold, especially in your arms and legs.
  - You feel dizzy or lightheaded.
  - You have a fast or irregular heartbeat.
- **Some people who have taken medicines like TRUVADA have developed serious liver problems called hepatotoxicity**, with liver enlargement (hepatomegaly) and fat in the liver (steatosis). **Call your healthcare provider right away if you get the following signs or symptoms of liver problems.**
  - Your skin or the white part of your eyes turns yellow (jaundice).
  - Your urine turns dark.
  - Your bowel movements (stools) turn light in color.
  - You don't feel like eating food for several days or longer.
  - You feel sick to your stomach (nausea).
  - You have lower stomach area (abdominal) pain.
- **You may be more likely to get lactic acidosis or liver problems** if you are female, very overweight (obese), or have been taking nucleoside analog medicines, like TRUVADA, for a long time.

- **If you are also infected with the hepatitis B virus (HBV),** you need close medical follow-up for several months after stopping treatment with TRUVADA. Follow-up includes medical exams and blood tests to check for HBV that could be getting worse. **Patients with hepatitis B virus infection, who take TRUVADA and then stop it, may get "flare-ups" of their hepatitis. A "flare-up" is when the disease suddenly returns in a worse way than before.**

What is TRUVADA?

TRUVADA is a type of medicine called an HIV-1 (human immunodeficiency virus) nucleoside analog reverse transcriptase inhibitor (NRTI). TRUVADA contains 2 medicines, EMTRIVA® (emtricitabine) and VIREAD® (tenofovir disoproxil fumarate, or tenofovir DF) combined in one pill. TRUVADA is always used with other anti-HIV-1 medicines to treat people with HIV-1 infection. TRUVADA is for adults and pediatric patients 12 years of age and older. TRUVADA has not been studied in children under age 12 or weighing less than 35 kg (77 lb) or in adults over age 65.

HIV infection destroys $CD4^+$ T cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

TRUVADA helps block HIV-1 reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV-1 to multiply. TRUVADA lowers the amount of HIV-1 in the blood (viral load). TRUVADA may also help to increase the number of T cells ($CD4^+$ cells). Lowering the amount of HIV-1 in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

TRUVADA does not cure HIV-1 infection or AIDS. The long-term effects of TRUVADA are not known at this time. People taking TRUVADA may still get opportunistic infections or other conditions that happen with HIV-1 infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium complex* (MAC) infection. **It is very important that you see your healthcare provider regularly while taking TRUVADA.**

TRUVADA does not lower your chance of passing HIV-1 to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

Who should not take TRUVADA?

- Do not take TRUVADA if you are allergic to TRUVADA or any of its ingredients. The active ingredients of TRUVADA are emtricitabine and tenofovir DF. See the end of this leaflet for a complete list of ingredients.
- Do not take TRUVADA if you are already taking ATRIPLA®, Combivir (lamivudine/zidovudine), EMTRIVA, Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine), or VIREAD because these medicines contain the same or similar active ingredients.

- Do not take TRUVADA to treat your HIV infection if you are also taking HEPSERA® to treat your HBV infection.

What should I tell my healthcare provider before taking TRUVADA?

Tell your healthcare provider if you:

- **are pregnant or planning to become pregnant.** We do not know if TRUVADA can harm your unborn child. You and your healthcare provider will need to decide if TRUVADA is right for you. If you use TRUVADA while you are pregnant, talk to your healthcare provider about how you can be on the TRUVADA Antiviral Pregnancy Registry.
- **are breast-feeding.** You should not breast feed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, it is not known if TRUVADA can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.
- **have kidney problems or are undergoing kidney dialysis treatment.**
- **have bone problems.**
- **have liver problems including hepatitis B virus infection.**

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take:

- Videx, Videx EC (didanosine). Tenofovir DF (a component of TRUVADA) may increase the amount of Videx in your blood. **You may need to be followed more carefully if you are taking TRUVADA and Videx together**. Also, the dose of didanosine may need to be reduced.
- Reyataz (atazanavir sulfate) or Kaletra (lopinavir/ritonavir). These medicines may increase the amount of tenofovir DF (a component of TRUVADA) in your blood, which could result in more side effects. You may need to be followed more carefully if you are taking TRUVADA and Reyataz or Kaletra together. TRUVADA may decrease the amount of Reyataz in your blood. If you are taking TRUVADA and Reyataz together, you should also be taking Norvir (ritonavir).

Keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers and pharmacist **every** time you visit your healthcare provider or fill a prescription.

How should I take TRUVADA?

- Take TRUVADA exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label.
- The usual dose of TRUVADA is 1 tablet once a day. TRUVADA is always used with other anti-HIV-1 medicines. If you have kidney problems, you may need to take TRUVADA less often.

- TRUVADA may be taken with or without a meal. Food does not affect how TRUVADA works. Take TRUVADA at the same time each day.
- If you forget to take TRUVADA, take it as soon as you remember that day. **Do not** take more than 1 dose of TRUVADA in a day. **Do not** take 2 doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do. **It is important that you do not miss any doses of TRUVADA or your anti-HIV-1 medicines.**
- When your TRUVADA supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to TRUVADA and become harder to treat.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider's care when taking TRUVADA.
- If you take too much TRUVADA, call your local poison control center or emergency room right away.

What should I avoid while taking TRUVADA?

- **Do not breast-feed.** See "What should I tell my healthcare provider before taking TRUVADA?"
- **Avoid doing things that can spread HIV infection** since TRUVADA does not stop you from passing the HIV infection to others.
  - **Do not share needles or other injection equipment.**
  - **Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.**
  - **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom or other barrier to reduce the chance of sexual contact with semen, vaginal secretions, or blood.
- ATRIPLA, Combivir (lamivudine/zidovudine), EMTRIVA, Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trizivir (abacavir sulfate/lamivudine/zidovudine), or VIREAD.
  TRUVADA should not be used with these medicines.
- TRUVADA should not be used with HEPSERA.

What are the possible side effects of TRUVADA?

TRUVADA may cause the following serious side effects (see "What is the most important information I should know about TRUVADA?"):

- **Lactic acidosis** (buildup of an acid in the blood). Lactic acidosis can be a medical emergency and may need to be treated in the hospital. **Call your doctor right away if you get signs of lactic acidosis.** (See "What is the most important information I should know about TRUVADA?")

- **Serious liver problems (hepatotoxicity),** with liver enlargement (hepatomegaly) and fat in the liver (steatosis). Call your healthcare provider right away if you get any signs of liver problems. (See "What is the most important information I should know about TRUVADA?")
- **"Flare-ups" of hepatitis B virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking TRUVADA. Your healthcare provider will monitor your condition for several months after stopping TRUVADA if you have both HIV-1 and HBV infection. TRUVADA is not approved for the treatment of hepatitis B virus infection. If you have advanced liver disease and stop treatment with TRUVADA, the "flare-up" of hepatitis B may cause your liver function to decline.
- **Kidney problems.** If you have had kidney problems in the past or take other medicines that can cause kidney problems, your healthcare provider should do regular blood tests to check your kidneys.
- **Changes in bone mineral density (thinning bones).** Laboratory tests show changes in the bones of patients treated with VIREAD, a component of TRUVADA. Some HIV patients treated with VIREAD developed thinning of the bones (osteopenia) which could lead to fractures. If you have had bone problems in the past, your healthcare provider may need to do tests to check your bone mineral density or may prescribe medicines to help your bone mineral density. Additionally, bone pain and softening of the bone (which may contribute to fractures) may occur as a consequence of kidney problems.

Other side effects with TRUVADA when used with other anti-HIV-1 medicines include:

- Changes in body fat have been seen in some patients taking TRUVADA and other anti-HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effect of these conditions are not known at this time.
- In some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

The most common side effects of EMTRIVA or VIREAD when used with other anti-HIV-1 medicines are: diarrhea, dizziness, nausea, headache, fatigue, abnormal dreams, sleeping problems, rash, depression, and vomiting. Additional side effects are lactic acidosis, kidney problems (including decline or failure of kidney function), inflammation of the pancreas, inflammation of the liver, allergic reaction (including swelling of the face, lips, tongue, or throat), shortness of breath, pain, fatty liver, stomach pain, weakness, indigestion, intestinal gas, and high volume of urine and thirst caused by kidney problems. Muscle pain and muscle weakness, bone pain, and softening of the bone (which may contribute to fractures) as a consequence of kidney

problems have been reported. Skin discoloration (small spots or freckles) may also happen with TRUVADA.

These are not all the side effects of TRUVADA. If you have questions about side effects, ask your healthcare provider. Report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store TRUVADA?

- **Keep TRUVADA and all other medicines out of reach of children.**
- Store TRUVADA at room temperature 77 °F (25 °C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General information about TRUVADA:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRUVADA for a condition for which it was not prescribed. Do not give TRUVADA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRUVADA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about TRUVADA that is written for health professionals. For more information, you may also call 1-800-GILEAD-5 or access the TRUVADA website at www.TRUVADA.com.

Do not use TRUVADA if seal over bottle opening is broken or missing.

What are the ingredients of TRUVADA?

Active Ingredients: emtricitabine and tenofovir disoproxil fumarate

Inactive Ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The tablets are coated with Opadry II Blue Y-30-10701 containing FD&C Blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

℞ Only

July 2011

21-752-GS-024

Appendix 2. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Acid Reducing Agents: antacids	↓ EVG	EVG plasma concentrations are lower with antacids due to local complexation in the GI tract and not to changes in gastric pH. It is recommended to separate the QUAD STR and antacid administration by at least 2 hours. For information on other acid reducing agents (eg, H2-receptor antagonists and proton pump inhibitors).
Alpha 1-Adrenoreceptor Antagonist: alfuzosin	↑ alfuzosin	Alfuzosin is primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of alfuzosin, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR and alfuzosin is contraindicated.
Analeptics: modafinil	↓ EVG ↓ COBI	Coadministration of modafinil, a CYP3A inducer, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative analeptics should be considered.
Antiarrhythmics: amiodarone bepridil disopyramide flecainide systemic lidocaine mexiletine propafenone quinidine	↑ antiarrhythmics	Concentrations of these antiarrhythmic drugs may be increased when coadministered with COBI. Caution is warranted and clinical monitoring is recommended upon coadministration of these agents with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Antibacterials: clarithromycin telithromycin	↑ clarithromycin ↑ telithromycin ↑ COBI	Concentrations of clarithromycin and/or COBI may be altered with coadministration of the QUAD STR. No dose adjustment of clarithromycin is required for patients with normal renal function or mild renal impairment (eGFR 60–90 mL/min). Clinical monitoring is recommended for patients with eGFR < 90 mL/min. For patients with eGFR < 60 mL/min, alternative antibacterials should be considered. Concentrations of telithromycin and/or COBI may be altered with coadministration of the QUAD STR. Clinical monitoring is recommended upon coadministration with the QUAD STR.
Anticoagulants: warfarin	↑ or ↓ warfarin	Concentrations of warfarin may be affected upon coadministration with the QUAD STR. It is recommended that the international normalized ratio (INR) be monitored upon coadministration with the QUAD STR.
Anticonvulsants: carbamazepine oxcarbazepine Phenobarbital phenytoin clonazepam ethosuximide	↓ EVG ↓ COBI ↑ clonazepam ↑ ethosuximide	Coadministration of phenobarbital, phenytoin, carbamazepine, and oxcarbazepine, CYP3A inducers, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative anticonvulsants should be considered. Concentrations of clonazepam and ethosuximide may be increased when coadministered with COBI. Clinical monitoring is recommended upon coadministration with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Antidepressants: selective serotonin reuptake inhibitors (SSRIs) trazodone	↑ SSRIs ↑ trazodone	Concentrations of these antidepressant agents may be increased when coadministered with COBI. Dose titration may be required for most drugs of the SSRI class. Concentrations of trazodone may increase upon coadministration with COBI. Dose reduction should be considered when trazodone is coadministered with the QUAD STR.
Antifungals: itraconazole ketoconazole voriconazole	↑ antifungals ↑ COBI	Concentrations of ketoconazole and/or COBI may increase with coadministration of the QUAD STR. When administering with the QUAD STR, the maximum daily dose of ketoconazole should not exceed 200 mg per day. Concentrations of itraconazole and voriconazole may be increased when coadministered with COBI. Clinical monitoring may be needed upon coadministration with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Anti-gout: colchicine	↑ colchicine	The QUAD STR should not be coadministered with colchicine to patients with renal or hepatic impairment. Treatment of gout-flares – coadministration of colchicine in patients on the QUAD STR: 0.6 mg (1 tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. Prophylaxis of gout-flares – coadministration of colchicine in patients on the QUAD STR: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. Treatment of familial Mediterranean fever – coadministration of colchicine in patients on the QUAD STR: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimycobacterial: rifabutin rifampin rifapentine	↓ EVG ↓ COBI	Coadministration of rifampin, rifabutin, and rifapentine, potent CYP3A inducers, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of the QUAD STR with rifampin, rifabutin, and rifapentine are contraindicated.
Beta-Blockers: metoprolol timolol	↑ beta-blockers	Concentrations of beta-blockers may be increased when coadministered with COBI. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Calcium Channel Blockers: amlodipine diltiazem felodipine nicardipine nifedipine verapamil	↑ calcium channel blockers	Concentrations of calcium channel blockers may be increased when coadministered with COBI. Caution is warranted and clinical monitoring is recommended upon coadministration with the QUAD STR.
Systemic Corticosteroids: dexamethasone fluticasone	↓ EVG ↓ COBI ↑ fluticasone	Coadministration of dexamethasone, a CYP3A inducer, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of fluticasone propionate and the QUAD STR is not recommended unless the potential benefit to the patient outweighs the risks of systemic corticosteroid side effects. Alternative corticosteroids should be considered. Coadministration of inhaled or oral corticosteroid with the QUAD STR is not recommended unless the potential benefit to the patient outweighs the risks.
Endothelin Receptor Antagonists: bosentan	↑ bosentan ↓ EVG ↓ COBI	Coadministration with the QUAD STR may lead to decreased EVG and/or COBI exposures and loss of therapeutic effect. Coadministration is not recommended.
Ergot Derivatives: dihydroergotamine ergonovine ergotamine methylergonovine	↑ ergot derivatives	Ergot derivatives are primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of these drugs, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR and dihydroergotamine, ergonovine, ergotamine, and methylergonovine are contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
GI Motility Agents: cisapride	↑ cisapride	Cisapride is primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of cisapride, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR and cisapride is contraindicated.
Herbal Products: St. John's wort (Hypericum perforatum)	↓ EVG ↓ COBI	Coadministration of St. John's wort, a potent CYP3A inducer, may significantly decrease COBI and EVG plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Coadministration of the QUAD STR with St. John's wort is contraindicated.
HMG CoA Reductase Inhibitors: atorvastatin lovastatin rosuvastatin simvastatin	↑ HMG-CoA reductase inhibitors	HMG CoA reductase inhibitors are primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of lovastatin or simvastatin, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR with lovastatin and simvastatin are contraindicated. Concentrations of atorvastatin may be increased when coadministered with EVG and COBI. Start with the lowest possible dose of atorvastatin with careful monitoring upon coadministration with the QUAD STR. Concentrations of rosuvastatin are transiently increased when coadministered with EVG and COBI. Dose modifications are not necessary when rosuvastatin is administered in combination with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Hormonal Contraceptives: norgestimate/ethinyl estradiol	↑ norgestimate ↓ ethinyl estradiol	Coadministration of the QUAD STR and a norgestimate/ethinyl estradiol-containing hormonal oral contraceptive resulted in decreased plasma concentrations of ethinyl estradiol and an increase in norgestimate. Use caution when coadministering the QUAD STR and a hormonal contraceptive. The hormonal contraceptive should contain at least 30 mcg of ethinyl estradiol. The long-term effects of substantial increases in progesterone exposure are unknown. Coadministration of the QUAD STR with oral contraceptives or hormonal contraceptives containing progestogens other than norgestimate, or less than 25 mcg of ethinyl estradiol, has not been studied.
Immunosuppressants: cyclosporine rapamycin sirolimus tacrolimus	↑ immunosuppressants	Concentrations of these immunosuppressant agents may be increased when coadministered with COBI. Therapeutic monitoring is recommended upon coadministration with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration with the QUAD STR may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of salmeterol and the QUAD STR is not recommended.
Neuroleptics: perphenazine pimozide risperidone thioridazine	↑ neuroleptics	Pimozide is primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of pimozide, which is associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR with pimozide is contraindicated. For other neuroleptics, consider reducing the dose of the neuroleptic upon coadministration with the QUAD STR.
Phosphodiesterase-5 (PDE5) Inhibitors: sildenafil tadalafil vardenafil	↑ PDE5 inhibitors	PDE5 inhibitors are primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of sildenafil and tadalafil, which may result in PDE5 inhibitor-associated adverse reactions. Coadministration of the QUAD STR with sildenafil and tadalafil for the treatment of pulmonary arterial hypertension are contraindicated. For the treatment of erectile dysfunction, it is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered with the QUAD STR.

Concomitant Drug Class: Drug Name	Effect on Concentrationa	Clinical Comment
Sedative/Hypnotics: buspirone clorazepate diazepam estazolam flurazepam orally-administered midazolam triazolam zolpidem	↑ sedatives/hypnotics	Midazolam and triazolam are primarily metabolized by CYP3A. Coadministration with the QUAD STR may result in increased plasma concentrations of these drugs, which are associated with the potential for serious and/or life-threatening reactions. Coadministration of the QUAD STR and orally administered midazolam and triazolam are contraindicated. With other sedative/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.

Note, this table is not all inclusive.

a ↑ = increase, ↓ = decrease

Appendix 3. Prespecified Statistical Methods for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

Efficacy

The ITT analysis set was the primary analysis set for efficacy analyses in the randomized phase for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103. Subjects were analyzed according to randomized treatment group (QUAD or comparator).

Study GS-US-236-0104

The primary efficacy endpoint in GS-US-236-0104 was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24. The primary analysis for the primary efficacy endpoint was the M=F method; secondary analyses used the M=E methods. The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL) weighted difference in the response rate and its 95% CI were calculated based on Mantel-Haenszel (MH) proportion.

The following secondary endpoints were analyzed using the same methods as for the primary efficacy endpoint: the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (M=F and M=E) and virologic outcomes at Weeks 24 and 48 using snapshot analysis. The change from baseline in CD4 cell count was summarized by using descriptive statistics. The difference in change from baseline in CD4 cell count between randomized treatment groups and the associated 95% CI were constructed using ANOVA, including baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) stratum in the model.

Studies GS-US-236-0102 and GS-US-236-0103

The primary efficacy endpoint in Studies GS-US-236-0102 and GS-US-236-0103 was the percentage of subjects with virologic success (ie, HIV-1 RNA < 50 copies/mL) at Week 48 using the FDA-defined snapshot analysis; TLOVR using the FDA-defined algorithm was the secondary endpoint. The percentage of subjects with virologic success at Week 48 was used to assess treatment noninferiority of the QUAD STR compared with the comparator using a conventional 95% CI approach, with a noninferiority margin of 12%. The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL)-weighted difference in the response rate and its 95% CI were calculated based on stratum-adjusted MH proportion. If the noninferiority of the QUAD STR was established, superiority testing was to be conducted between treatments using the same 95% CI. Supporting analyses of the primary endpoint included sensitivity analyses to evaluate effects of study drug discontinuations not related to virologic response and late discontinuations, and subgroup analyses to assess treatment differences between specified subgroups (ie, age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, and study drug adherence).

The following secondary and tertiary endpoints were analyzed using the same methods as for the primary efficacy endpoint: The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (M=F and M=E) and virologic outcomes at 48 using the FDA-defined TLOVR algorithm (secondary endpoint) and HIV-1 RNA < 50 copies/mL (tertiary endpoint) were

analyzed using the same methods as for the primary efficacy endpoint. The change from baseline in CD4 cell count (tertiary endpoint) was summarized by using descriptive statistics. The difference in change from baseline in CD4 cell count between randomized treatment groups and the associated 95% CI were constructed using ANOVA, including baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) stratum in the model.

Safety

The safety analysis set in Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103 included all subjects who were randomized and received at least 1 dose of study drug. Safety was assessed during the study by clinical laboratory tests, physical examinations at various time points during the study, and by documentation of AEs and concomitant medications. All safety data collected on or after the date that study drug was first administered up to 30 days after the last dose of study drug was summarized by treatment group using the safety analysis set. Data were summarized by treatment using descriptive statistics.

Pooled Data for Studies GS-US-236-0104, GS-US-236-0102, and GS-US-236-0103

Individual and pooled analyses from Studies GS-US-236-0102 and GS-US-236-0103 up to the Week 48 cutoff dates and Study GS-US-236-0104 up to Week 60 (unblinding visit) are presented.

Snapshot Analysis Algorithm

In the FDA-defined snapshot analysis for the Week 48 virologic outcome, the analysis window was defined from Study Days 309 to 378 (inclusive). All the HIV-1 RNA data collected on treatment (prior to or on the last dose date of study drug) were used in the snapshot analysis. Virologic outcome was defined as the following categories:

- **Virologic Success:** included subjects who had their last available HIV-1 RNA value < 50 copies/mL in the Week 48 analysis window while on randomized treatment

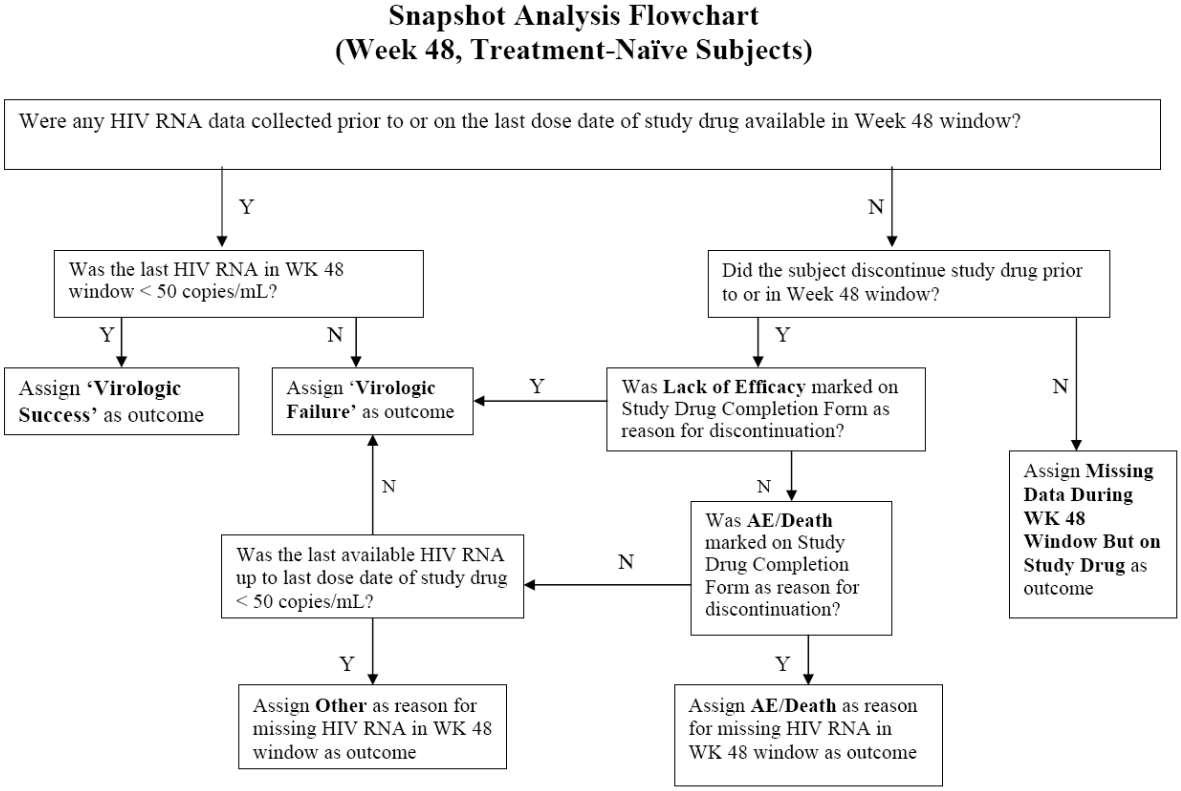
- **Virologic Failure:** included subjects who had their last available HIV-1 RNA value ≥ 50 copies/mL in the Week 48 analysis window while on randomized treatment; or who did not have on-treatment HIV-1 RNA data in the Week 48 analysis window due to: 1) discontinuation of study drug for lack of efficacy; or 2) discontinuation of study drug for reasons other than an AE, death, or lack of efficacy and their last available HIV-1 RNA value on treatment was ≥ 50 copies/mL

- **No Virologic Data in the Week 48 Analysis Window:** included subjects who did not have on-treatment HIV-1 RNA data in the Week 48 analysis window because: 1) study drug was discontinued due to AE or death (regardless of last available HIV-1 RNA result); 2) study drug was discontinued due to reasons other than AE/death and lack of efficacy (eg, withdrew consent, lost to follow-up) and the last available HIV-1 RNA value on treatment was < 50 copies/mL; or 3) subjects had missing data during the window, but remained on study drug

The flowchart of snapshot analysis algorithm is provided below in Appendix Figure 1.

Appendix Figure 1. Flowchart of Snapshot Analysis Algorithm

The following flowchart for snapshot analysis algorithm is based on the FDA Fax communication document for snapshot analysis for IND 101, 283 (30 March 2010).



TLOVR Algorithm

The outcome variable for the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 48 (responder) was derived using all available nonmissing HIV-1 RNA data (including unscheduled data, post-Week 48 data, and 30-day follow-up data), based on the FDA-defined TLOVR algorithm {5059}, described below.

To be classified as a responder, a subject had to satisfy the following 3 conditions:

- Achieved a confirmed suppression (ie, HIV-1 RNA < 50 copies/mL on 2 consecutive visits) prior to or on the upper limit of the Week 48 analysis window

- Did not die or prematurely discontinue study drug prior to or on the upper limit of the Week 48 analysis window

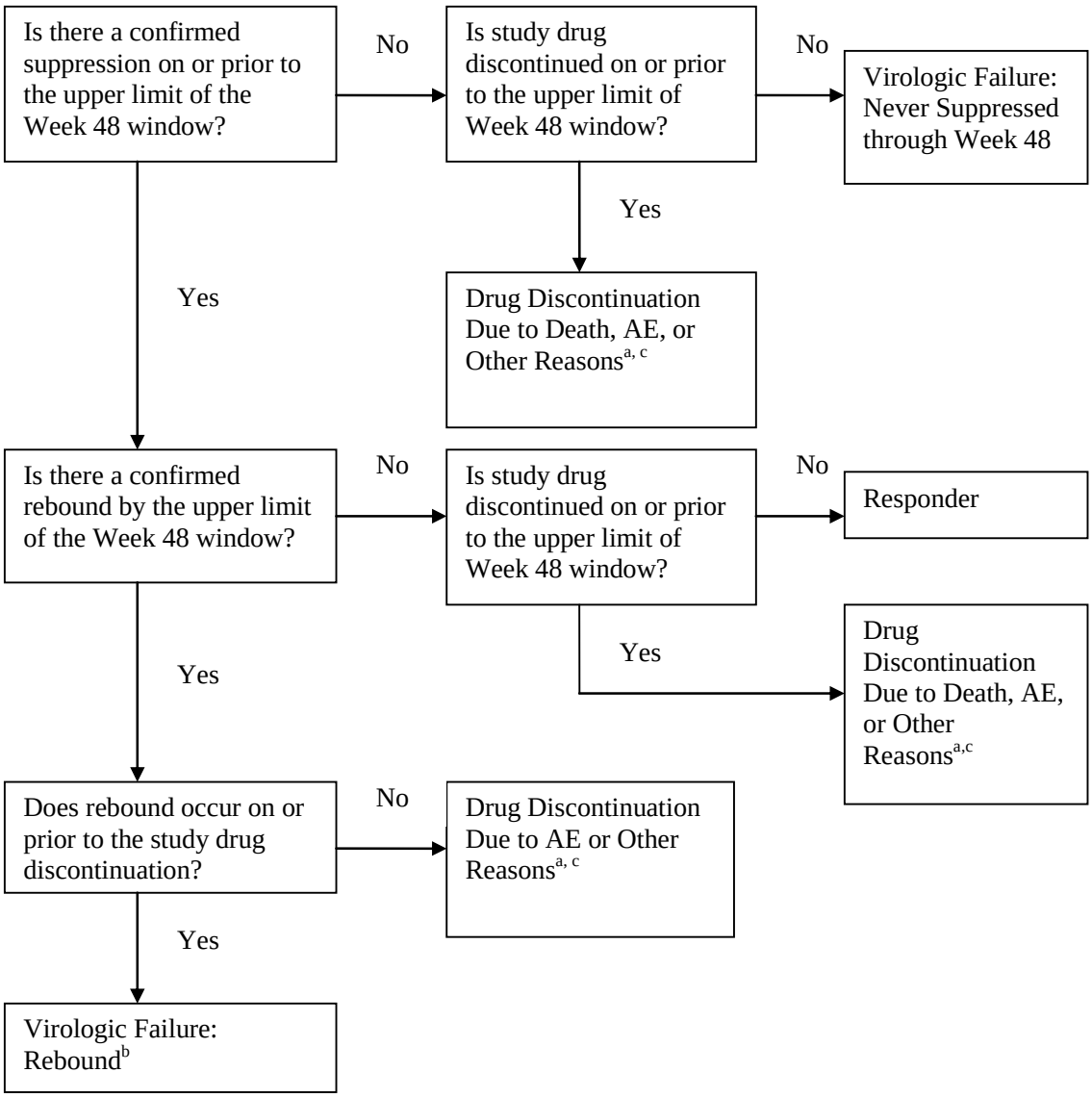
- Did not have a confirmed rebound (ie, HIV-1 RNA ≥ 50 copies/mL at 2 consecutive visits or last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study drug) by the upper limit of the Week 48 analysis window after achieving confirmed suppression

For confirming viral suppression or rebound, the first HIV-1 RNA must have occurred on or prior to the upper limit of the Week 48 analysis window. The confirming event (ie, the second of the consecutive HIV-1 RNA values or premature study drug discontinuation) could have occurred after the upper limit of the Week 48 analysis window.

- Subjects who met the above 3 criteria were classified as a responder at Week 48; otherwise, subjects were considered as nonresponders at Week 48.

The flow chart for assigning TLOVR outcomes is provided below in Appendix Figure 2.

Appendix Figure 2. Flowchart of TLOVR Outcome at Week 48 (Treatment-Naive Subjects)



Appendix 4. Studies GS-US-236-0102 and GS-US-236-0103: Pooled Listing of Subjects with Emergent HIV-1 Resistance at Week 48 (N = 21)

Subject Number	Treatment Group	Baseline HIV-1 RNA (copies/mL)	HIV-1 Subtype	Time of Virology Analysis	Emergent Mutations			Drug Susceptibility (Fold-Change from Wild-Type)[a]			
					INSTI[b]	NNRTI[c]	NRTI[d]	EVG	EFV	FTC	TFV
(b) (6)	QUAD	200,000	B	W40	H51H/Y, L68V, E92Q	—	A62A/V, K65R, M184V	149	0.45	> 88	1.49
	QUAD	234,000	B	W32[e]	E92Q, S153A	—	K65R, M184V	111	0.35	> 108	1.21
	QUAD	364,000	B	W32	E92E/Q, Q148Q/R, N155H/N	—	M184V	51	0.83	> 108	0.72
	QUAD	31,000	B	W48	E92Q	—	M184V	44	0.72	> 121	0.46
	QUAD	2,620,000	B	W16	E92Q	—	M184V	36	0.75	> 75	0.46
	QUAD	172,000	B	W24	E92Q	—	M184I	28	1.08	> 103	0.48
	QUAD	183,000	B	W40	T66T/I, E92E/Q	—	M184V	5.55	1.37	> 152	0.64
	QUAD	107,000	B	W24[e]	—	—	K65K/R, M184M/I	1.78	0.67	116	0.67
	QUAD	560,000	B	W32	G140C, Q148R	—	A62A/V, K65R, M184V	> 198	0.95	> 84	1.59
	QUAD	258,000	B	W24	N155H	—	M184V	36	1.02	> 126	0.54
	QUAD	540,000	B	W16	Q148R	—	M184V	23	0.79	> 126	0.74
	QUAD	75,300	B	ESDD (W20)	T66I/T, E92E/Q, N155N/H, E157E/Q	nd	nd	54	nd	nd	nd
	QUAD	210,000	B	W12[e]	—	—	M184V	1.05	0.53	> 88	0.44
	ATR	184,000	B	W48	—	K103N. M230L	K65R, M184M/I	1.30	> 70	> 129	1.75

Subject Number	Treatment Group	Baseline HIV-1 RNA (copies/mL)	HIV-1 Subtype	Time of Virology Analysis	Emergent Mutations			Drug Susceptibility (Fold-Change from Wild-Type)[a]			
					INSTI[b]	NNRTI[c]	NRTI[d]	EVG	EFV	FTC	TFV
(b) (6)	ATR	99,000	B	W48	—	K103N/K, Y188Y/F/H/L	—	nd	68	1.10	1.07
	ATR	19,700	B	W8	—	K103N	—	1.53	43	0.82	1.14
	ATR	4860	B	W48	—	K103N	—	1.49	19.4	0.99	1.02
	ATR	955,000	B	W32	—	K103N, V108I	K65R, M184M/V	0.97	18.7	42	1.36
	ATR	23,700	B	W48	—	V90V/I, K101E/K, K103K/N, V108V/I, M230M/L	—	1.26	7.05	1.07	0.78
	ATR	12,200	B	W24	—	K101E/K, K103N/S, G190A/G	—	1.27	6.49	1.20	0.97
	ATR	140,000	B	W48	—	K101E/K	—	1.29	1.26	1.03	0.91

—, no mutations developed; EFV, efavirenz; EVG, elvitegravir; ESDD, early study drug discontinuation; FTC, emtricitabine; IN, integrase; INSTI, integrase strand-transfer inhibitor; INSTI-R, integrase strand-transfer inhibitor resistance; nd, no phenotype was available due to assay failure; NNRTI, nonnucleoside reverse transcriptase inhibitor; NNRTI-R, nonnucleoside reverse transcriptase inhibitor resistance; NRTI, nucleoside reverse transcriptase inhibitor; NRTI-R, nucleoside reverse transcriptase inhibitor resistance; RT, reverse transcriptase; W, week

a Shaded cells represent a PhenoSense fold-change value greater than or equal to the biological or clinical cutoff for each drug.

b Primary INSTI-R mutations are T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, and N155H/S. Other INSTI-R mutations are H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K. A cumulative list of mutations that developed is shown.

c NNRTI-R mutations are V90I, A98G, L100I, K101E/H/P, K103N, V106A/M/I, V108I, E138A, V179D/F/T, Y181C/I/V, Y188L/C/H, G190A/S, P225H, and M230L in RT. A cumulative list of mutations that developed is shown.

d Nucleoside reverse transcriptase inhibitor resistance (NRTI-R) mutations are M41L, E44D, A62V, K65R, D67N, T69D, T69 Insertions; K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, and K219Q/N/E/R in RT. A cumulative list of mutations that developed is shown.

e Subject (b) (6) had IN data from Week 32 and assay failure at Week 48. Protease/RT data were obtained from Week 48 and had assay failure at Week 32. Subject (b) (6) had IN data from Week 16 and assay failure at Week 24. Protease/RT data were obtained from Weeks 16 and 24. Subject (b) (6) had protease/RT data at Week 12 but IN assay failure; the Week 8 sample was used for analysis of IN.

Appendix 5. Studies GS-US-236-0102 and GS-US-236-0103: Summary Details of Subjects Who Discontinued Study Drug Due to Renal Adverse Events

Subject No.	Group	Contributory History[a], Concomitant Medications, and Screening or Baseline Laboratory Tests	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
Study GS-US-236-0102					
(b) (6)	QUAD	Concomitant acyclovir; baseline Cr 1.04, eGFR 91.28	Renal failure (D169–D214)	DC (D198)	Maximum Cr 1.49 (eGFR 69.07) (D193). After discontinuation of QUAD, Cr improved, ranging from 0.90 to 1.30 (eGFR 110.98 to 79.17). Since the Week 48 data cut, serum creatinine remains stable at baseline level. Post-DC regimen EFV, ABC/3TC was started on D199.
	QUAD	Hypertension and hypercholesterolemia; concomitant amlodipine and ramipril; screening Cr 1.30, eGFR 66.77	Renal failure (D59–cont.)	DC (D66)	Maximum Cr 2.86 (eGFR 31.82) (D59) with +2 proteinuria. After discontinuation of QUAD, Cr improved and proteinuria normalized within a few weeks. Subsequent Cr ranged from 2.37 to 1.49 (eGFR 38.64 to 64.52). Since the Week 48 data cut, Cr remains stable and proteinuria completely resolved. Post-DC regimen ATV/r, ABC/3TC was started on D164.

Subject No.	Group	Contributory History[a], Concomitant Medications, and Screening or Baseline Laboratory Tests	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
(b) (6)	QUAD	History of renal disease, hypertension and hypercholesterolemia; concomitant quinapril and simvastatin use; baseline Cr 1.52, eGFR 68.27	Blood creatinine increased (D16–cont.)	DC (D37)	Maximum Cr 4.47 (eGFR 23.94) with +3 glycosuria and +1 proteinuria (D44). After discontinuation of QUAD, all laboratory abnormalities improved with Cr ranging from 2.85 to 1.42 (eGFR 38.01 to 80.59) and proteinuria and glycosuria normalized. TFV C_{max} and AUC were 3.1- and 4.5-fold higher than the median value of QUAD subjects in the PK substudy. Since the Week 48 data cut, serum creatinine remains stable and urine remains negative for glycosuria and proteinuria. Post-DC regimen DRV/r, RAL was started on D168.
	QUAD	Concomitant acyclovir use; screening Cr 1.26, eGFR 114.81, +1 proteinuria	Fanconi syndrome acquired (D284–cont. at the time of last study visit on Week 48)	DC (D323)	Cr 1.81 (eGFR 79.55) with +4 glycosuria, +2 proteinuria, and phosphate 1.8 (FE_{PO4} 51.4%) (D284). After discontinuation of QUAD, all laboratory abnormalities improved except proteinuria, with Cr ranging 1.54 to 1.70 (eGFR 90.87 to 82.32). There are no further data after Week 48 data cut due to subject's withdrawal of consent on D381, except last reported Cr from a local lab of 1.4 at Week 60.
	QUAD	Baseline Cr 1.00, eGFR 82.33	Blood creatinine increased (D399–cont.)	DC (D411)	Maximum Cr 1.65 (eGFR 49.38) with +2 glycosuria and +2 proteinuria (D399). After discontinuation of QUAD, all laboratory abnormalities improved, with Cr ranging from 1.61 to 1.31 (eGFR 50.30 to 73.18). Since the Week 48 data cut, both glycosuria and proteinuria completely resolved. Post-DC regimen RPV, ABC/3TC was started on D415.

Subject No.	Group	Contributory History[a], Concomitant Medications, and Screening or Baseline Laboratory Tests	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
Study GS-US-236-0103					
(b) (6)	QUAD	History of proteinuria and hematuria; concomitant amiloride/hydrochlorothiazide (moduretic); screening Cr 1.03, eGFR 99.42; +3 proteinuria at baseline	Blood creatinine increased (D81–D277)	DC (D120)	Cr 1.35 (eGFR 75.37) with +2 proteinuria (D81). After discontinuation of QUAD and Week 48 data cut, Cr remained elevated at 1.45 to 1.20 (eGFR 71.84) and proteinuria persisted (+1 to +2). New AE of hypertension (Day 25). Post-DC regimen DRV/r, ZDV/3TC was started on D121.
	ATV/r	History of diabetes mellitus type 2, hypertension, and hypercholesteremia; concomitant atenolol, glipizide, hydralazine, lisinopril, sitagliptin, and amlodipine; screening Cr 0.96, eGFR 102.05	Nephropathy toxic (D230-D268)	DC (D262)	Maximum Cr 1.45 (eGFR 60.28) (D230). Mostly persistent proteinuria (+1 to +2). After discontinuation of ATV/r+TVD, Cr returned to baseline, ranging from 1.07 to 0.88 (eGFR 87.54 to 107.32). Since the Week 48 data cut, Cr normalized at 0.89 and +1 proteinuria persists. Post-DC regimen ATV/r, ABC/3TC was started on D273.
	ety Update				
	QUAD	Screening Cr 1.16, eGFR 105.26	Blood creatinine increased (D337–cont)	DC (D422)	Maximum Cr 1.66 (eGFR 71.95) (D337) with intermittent +1 proteinuria (D29, 57, 222). After discontinuation of QUAD, Cr improved to 1.39 (eGFR 86.70) and proteinuria was trace. Post-DC regimen RPV, ABC/3TC was started on D424.

3TC, lamivudine; ABC, abacavir; AE, adverse event; ATV/r, ritonavir-boosted atazanavir; AUC, area under the plasma concentration-time curve; C_{max}, maximum observed concentration; Cr, serum creatinine; D, study day; DC, discontinuation of study drug; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; PK, pharmacokinetic; QUAD, EVG/COBI/FTC/TDF; RAL, raltegravir; RPV, rilpivirine; TFV, tenofovir; TVD, Truvada; ZDV, zidovudine

a Includes medical conditions, AEs, laboratory findings, and medications of potential relevance to renal abnormalities.

Appendix 6. Studies GS-US-216-0105 and GS-US-216-0114: Summary Details of Subjects Who Discontinued Study Drug Due to Renal Adverse Events

Subject No.	Group	Renal AE (Onset)	Medical History, Concomitant Medications, and Screening or Baseline Laboratory Tests[a, b]	Study Drug Status (Reason for and Day of Discontinuation)	Clinical Course
Study GS-US-216-0114					
(b) (6)	ATV/co+TVD	Fanconi Syndrome acquired (D85)	None; screening Cr=0.77 mg/dL, $eGFR_{CG}$=90.36 mL/min	DC (renal SAE; D118)	Maximum Cr=0.94 mg/dL ($eGFR_{CG}$=70.55 mL/min) with glycosuria, proteinuria, and hypophosphatemia (D113). After study drug discontinuation (D118), Cr improved ranging from 0.71 to 0.89 mg/dL; all other abnormalities normalized.
	ATV/co+TVD	GFR rate abnormal (D57)	History of hypertension; baseline Cr=0.86mg/dL, $eGFR_{CG}$=69.95mL/min	DC (renal AE; D82)	Maximum Cr=1.32 mg/dL ($eGFR_{CG}$=43.85 mL/min). After study drug discontinuation (D82), Cr improved to 0.95 mg/dL (D113).
	ATV/co+TVD	Creatinine renal clearance decreased (D15; D83; D281; D337)	None; baseline Cr=1.02 mg/dL, $eGFR_{CG}$=99.98 mL/min	DC (renal AE; D345)	Maximum Cr=3.58 mg/dL ($eGFR_{CG}$=26.70 mL/min) (D342) with +1 glycosuria and +2 proteinuria (D337) and hypophosphatemia (2.0 mg/dL) (D342). After study drug discontinuation (D345), Cr improved from 3.01 mg/dL (D349) to 1.93 mg/dL (D378). All other abnormalities normalized.
	ATV/co+TVD	Blood creatinine increased (D425)	None; baseline Cr=1.03 mg/dL, $eGFR_{CG}$=122.37 mL/min	DC (renal AE; D450)	Maximum Cr=1.79 mg/dL ($eGFR_{CG}$=76.01 mL/min) with +2 proteinuria (D450). After study drug discontinuation (D450), and as of the data cut-off date, no further follow-up laboratory results available.

Subject No.	Group	Renal AE (Onset)	Medical History, Concomitant Medications, and Screening or Baseline Laboratory Tests[a, b]	Study Drug Status (Reason for and Day of Discontinuation)	Clinical Course
(b) (6)	ATV/co+TVD	Renal impairment (D341)	History of hyperprolactinemia; screening Cr=0.70 mg/dL, $eGFR_{CG}$=74.59 mL/min	DC (renal AE; D364)	Maximum Cr=1.19 mg/dL ($eGFR_{CG}$=43.75 mL/min) (D358) with +1 glycosuria and +2 proteinuria (D365). After study drug discontinuation (D364), Cr improved ranging from 0.94 to 0.98 mg/dL; glycosuria normalized and proteinuria improved to +1 (D426).
	ATV/co+TVD	Nephropathy (D176)	History of hepatitis C; baseline Cr=1.06 mg/dL, $eGFR_{CG}$=87.70 mL/min	DC (renal AE; D176)	Maximum Cr=5.07 mg/dL ($eGFR_{CG}$=16.60 mL/min) with +3 glycosuria and +2 proteinuria (D170). Concurrent AE of enterobacter sepsis (D176) and diabetes mellitus (D176). After study drug discontinuation (D176), Cr improved to 2.19 mg/dL (D211) (local laboratory). As of the data cut-off date, no further follow-up laboratory results available.
	ATV/r+TVD	Fanconi Syndrome acquired (D218)	History of hepatitis B; screening Cr 0.91mg/dL, $eGFR_{CG}$=72.59 mL/min	DC (renal AE; D237)	Maximum Cr 1.30 mg/dL ($eGFR_{CG}$=55.13 mL/min) with +2 glycosuria, +2 proteinuria, and hypophosphatemia (2.1 mg/dL) (D225). After study drug discontinuation (D237), Cr improved ranging from 1.03 to 1.17 mg/dL; all other abnormalities returned to baseline levels.

Subject No.	Group	Renal AE (Onset)	Medical History, Concomitant Medications, and Screening or Baseline Laboratory Tests[a, b]	Study Drug Status (Reason for and Day of Discontinuation)	Clinical Course
(b) (6)	ATV/r+TVD	Renal failure (D337)	None; baseline Cr 1.00 mg/dL, $eGFR_{CG}$=101.96 mL/min	DC (renal AE; D396)	Maximum Cr=1.59 mg/dL ($eGFR_{CG}$=69.16 mL/min) (D337) with +3 glycosuria, +2 proteinuria, and hypophosphatemia (1.6 mg/dL) (D397). Relevant AE of hyperglycemia (D114). After study drug discontinuation (D396), Cr improved ranging from 1.48 to 1.56 mg/dL; phosphate improved to 2.9 mg/dL and glycosuria and proteinuria improved to trace (D421).
	ATV/r+TVD	Renal impairment (D225)	Screening Cr 0.86 mg/dL, $eGFR_{CG}$=69.68 mL/min)	DC (renal AE; D268)	Maximum Cr=1.30 mg/dL ($eGFR_{CG}$=42.75 mL/min) (D235) with +1 proteinuria (D225). After study drug discontinuation (D268), Cr returned to screening level at 0.85 mg/dL and proteinuria normalized (D299).
	ATV/r+TVD	Blood creatinine increased (D254)	Screening Cr 1.29 mg/dL ($eGFR_{CG}$=81.40 mL/min)	DC (renal AE; D279)	Maximum Cr=1.58 mg/dL ($eGFR_{CG}$=66.27 mL/min) (D229). Concurrent AE of hepatitis C (D229). After study drug discontinuation (D279), Cr improved ranging from 1.40 to 1.43 mg/dL.

Subject No.	Group	Renal AE (Onset)	Medical History, Concomitant Medications, and Screening or Baseline Laboratory Tests[a, b]	Study Drug Status (Reason for and Day of Discontinuation)	Clinical Course
(b) (6)	ATV/r+TVD	Renal failure acute (D112)	History of diabetes mellitus, *Salmonella* bacteremia; on loxoprofen (Day 105–111); baseline Cr 0.59 mg/dL, $eGFR_{CG}$=100.68 mL/min, +3 glycosuria	DC (renal AE; D113)	Maximum Cr=12.53 mg/dL ($eGFR_{CG}$=4.56 mL/min) (D114) with +1 glycosuria and +1 proteinuria (D112). Concurrent AEs of gastroenteritis Salmonella (D109), spinal compression fracture (D112). After study drug discontinuation (D113), Cr improved ranging from 0.72 to 1.04 mg/dL; glycosuria normalized and proteinuria returned to baseline level of trace (D336).
Study GS-US-216-0105 (Double-Blind Phase)					
(b) (6)	ATV/r+TVD	Renal failure (D6)	History of cerebrovascular accident; cocaine abuse; hypertension; smoking; concomitant dyazine, and captopril; baseline Cr 1.23 mg/dL, $eGFR_{CG}$ =56.45 mL/min, +1 proteinuria	DC (subject was ineligible; D6)	Subject entered the study with decreased eGFR as a protocol violation; nonserious, Grade 2 renal failure reported on Day 6; study drug was discontinued

Subject No.	Group	Renal AE (Onset)	Medical History, Concomitant Medications, and Screening or Baseline Laboratory Tests[a, b]	Study Drug Status (Reason for and Day of Discontinuation)	Clinical Course
Study GS-US-216-0105 (Open-Label Phase)					
(b) (6)	ATV/r+→ ATV/co+TVD[c]	GFR decreased (D566)	History of *Pneumocystis carinii* pneumonia, diarrhea, and syphilis; concomitant trimethoprim/sulmathoxazole, ibuprofen, and terbinafine; baseline Cr=1.23 mg/dL, $eGFR_{CG}$=95.90 mL/min	DC (reported as GFR decreased, D566)	The subject completed ATV/r+TVD in the blinded treatment phase and initiated ATV/co+TVD on Study Day 400, after which the eGFR was clinically unchanged (at time of discontinuation Cr 1.35 mg/dL, $eGFR_{CG}$ 77.52 mL/min); the reason for study drug discontinuation is unclear as the subject had stable eGFR, no evidence of renal tubular compromise, and did not meet a protocol-defined endpoint that would require study drug interruption or discontinuation.

AE, adverse event; ATV/co, cobicistat-boosted atazanavir; ATV/r, ritonavir-boosted atazanavir; Cr, serum creatinine; D, study day; DC, discontinuation of study drug; eGFR, estimated glomerular filtration rate; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault equation; GFR, glomerular filtration rate; SAE, serious adverse event; TVD, Truvada

a Includes medical conditions, AEs, laboratory findings, and medications of potential relevance to renal abnormalities.

b For baseline Cr and $eGFR_{CG}$, the lower of either screening or baseline values are shown.

c Subject (b) (6) was randomized to ATV/r+TVD in the double-blind phase and switched to ATV/co+TVD in the open-label phase.